A Literature Review - Problem Definition Studies on Selected Toxic Chemicals

Volume 2 of 8

OCCUPATIONAL HEALTH AND SAFETY ASPECTS OF PHOSPHORUS SMOKE COMPOUNDS

Final Report - April, 1978

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Supported by

U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD-17-77-C-7020

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SCIENCE INFORMATION SERVICES DEPARTMENT
THE FRANKLIN INSTITUTE RESEARCH LABORATORIES
THE BENJAMIN FRANKLIN PARKWAY · PHILADELPHIA, PENNSYLVANIA 19103

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER

2. GOVT ACCESSION NO.

3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle)
A Literature Review - Problem Definition Studies on Selected Toxic Chemicals. Volume 2, OCCUPATIONAL HEALTH AND SAFETY ASPECTS OF PHOSPHORUS SMOKE COMPOUNDS.

5. TYPE OF REPORT & PERIOD COVERED
Final Report
March 1977 - April 1978

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)
Khizar Wasti, Ph.D. Principal Investigator
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8. CONTRACT OR GRANT NUMBER(s)
DAMD-17-77-C-7020

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Science Information Services Department
The Franklin Institute Research Laboratories
The Benjamin Franklin Parkway-Philadelphia, Pa. 19103

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
62720A
3E762720A835 00 030

11. CONTROLLING OFFICE NAME AND ADDRESS
U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

12. REPORT DATE
April 1978

13. NUMBER OF PAGES
104
104p.

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)

15. SECURITY CLASS. (of this report)
Unclassified

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; Distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Analysis	Carcinogenicity	Human toxicity
Animal toxicity	Chemical properties	Industrial hygiene
Biochemical changes	Epidemiology	Metabolism
Butyl rubber/red phosphorus	Epoxy white phosphorus	Mutagenicity
		Phosphoric acid

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This Problem Definition Study provides information on toxicological aspects and health hazards of phosphorus smoke compounds. The compounds covered in this study are red phosphorus, white phosphorus, butyl rubber/red phosphorus, plasticized white phosphorus, and epoxy white phosphorus. The subjects covered in this review are chemical and physical properties, toxicity, pharmacokinetics, sampling and analysis, industrial hygiene and safety practices, and standards. Recommendations for further toxicological studies on animals are also provided. There is virtually no information on the toxicity of butyl rubber/red phosphorus,

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

Unclassified

401 835

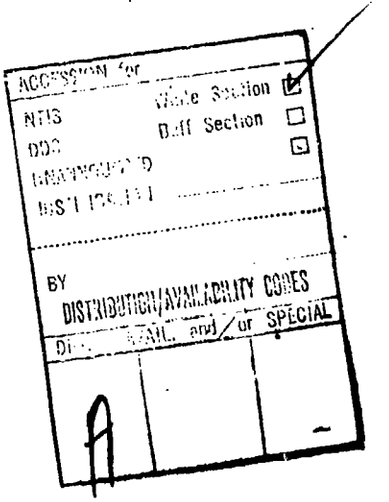
SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

19. KEY WORDS (Cont'd)

Phosphorus	Plasticized white phosphorus	Toxicity
Phosphorus pentcxide	Red phosphorus	White phosphorus
Phosphorus smoke	Safety practices	
Phosphorus vapors	Sampling	
Physical properties	Smoke	

20. ABSTRACT (cont'd)

plasticized white phosphorus, or epoxy white phosphorus. The toxicity of red phosphorus has not been studied very well. White phosphorus has been found to be highly toxic to both experimental animals and humans. Occupational exposure to white phosphorus vapors has produced necrosis of the jaw ("phossy jaw") among workers. There have been no reported cases of carcinogenicity in humans after white phosphorus intoxication. Tests for mutagenicity and teratogenicity have not been reported in the literature.



EXECUTIVE SUMMARY

This literature review (100 references) discusses the occupational health and safety of phosphorus smoke compounds which are used by the U.S. Armed Forces to produce smoke screens. These five compounds are white phosphorus, red phosphorus, butyl rubber/red phosphorus, butyl rubber/white phosphorus, and epoxy white phosphorus.

To make butyl rubber/red phosphorus, red phosphorus is combined with styrene-butadiene rubber (butyl rubber). White phosphorus also combines with styrene-butadiene rubber to make butyl rubber/white phosphorus, which is also called plasticized white phosphorus. Epoxy white phosphorus is made from white phosphorus and Bisphenol A-epichlorohydrin, an epoxy resin.

There are no acceptable reports on the dangers of red phosphorus to the health of humans or animals.

White phosphorus causes severe skin burns upon contact with the skin. Breathing white phosphorus vapors can damage the lungs and liver. If white phosphorus is eaten (children may eat it accidently in roach poison) it may cause garlic taste, vomiting and damage to the stomach and the rest of the digestive tract. Death may occur in 12 hours. If the person lives, after a few days the patient may sicken and begin vomiting again, and this means that there may be damage to the kidneys, liver and digestive tract.

When white phosphorus fumes are inhaled repeatedly, in industry, damage to the jawbone, teeth, and other bones is reported. Also there may be blood disorders and abnormal urine.

In animals, eating of white phosphorus causes liver damage and death. Placing it on skin of rabbits caused deaths to many of them in 3 days. It did not produce eye irritation or skin allergy in rabbits. Liver, kidney and blood changes occurred. Long-term animal studies with white phosphorus have caused retarded growth and damage to bones, liver, kidneys and brain. The ability of white phosphorus to produce cancer in animals, mutations in bacteria, or to harm unborn offspring is not known.

When smoke screens are made from burning phosphorus smoke compounds, humans who breathe the smoke may begin coughing, and develop sore throats, runny noses and may have trouble breathing after 15 minutes of breathing the smoke. They recover in a few days if they stop breathing smoke. In animal experiments, breathing the same smoke caused lung congestion, and liver and kidney damage.

Mice which breathed burning styrene-butadiene rubber died of asphyxiation from carbon monoxide. There are no experiments reported to test the hazards of breathing butyl rubber/phosphorus smoke screens, or the epoxy white phosphorus smoke screen. Also, there is no information on the ability of the butyl rubber/phosphorus or epoxy white phosphorus smoke to produce cancer, mutations or to harm unborn offspring.

In industries where persons work around white phosphorus, protection from burns to the eyes and skin is important. Gas masks are necessary to avoid breathing large amounts of white phosphorus fumes. White phosphorus is also a fire hazard because it will burn if it is exposed to room air. The fire can be extinguished with sand or water. Persons working with white phosphorus should be examined routinely for damage to the teeth and jawbone, and have blood and urine tests done.

ABSTRACT

This Problem Definition Study provides information on toxicological aspects and health hazards of phosphorus smoke compounds. The compounds covered in this study are red phosphorus, white phosphorus, butyl rubber/red phosphorus, plasticized white phosphorus, and epoxy white phosphorus. The subjects covered in this review are chemical and physical properties, toxicity, pharmacokinetics, sampling and analysis, industrial hygiene and safety practices, and standards. Recommendations for further toxicological studies on animals are also provided. There is virtually no information on the toxicity of butyl rubber/red phosphorus, plasticized white phosphorus, or epoxy white phosphorus. The toxicity of red phosphorus has not been studied very well. White phosphorus has been found to be highly toxic to both experimental animals and humans. Occupational exposure to white phosphorus vapors has produced necrosis of the jaw ("phossy jaw") among workers. There have been no reported cases of carcinogenicity in humans after white phosphorus intoxication. Tests for mutagenicity and teratogenicity have not been reported in the literature.

FOREWORD

The industrial hygiene and occupational health research program of the U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, Maryland was initiated in 1976 to study health problems and recommend criteria for occupational exposure to military-unique chemicals. This Problem Definition Study (PDS) has been prepared as part of the research program under contract number DAMD-17-77-C-7020 in order to provide the published data relating to occupational health and safety aspects of phosphorus smoke compounds. The phosphorus smoke compounds under review include butyl rubber/red phosphorus, epoxy white phosphorus, and plasticized white phosphorus; red and white phosphorus are also discussed. The topics covered in this PDS include chemistry of phosphorus, toxicity of phosphorus and its smoke to humans and animals, pharmacokinetic data, industrial hygiene and safety practices, and sampling and analysis of phosphorus in air and in biological media.

This Problem Definition Study is the second in a series of eight reports prepared under this contract.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF FIGURES AND TABLES

I. INTRODUCTION

Phosphorus smoke compounds are used by the military to produce smoke screens and signalling smokes. The compounds employed are butyl rubber/red phosphorus, plasticized white phosphorus, and epoxy white phosphorus. The main objective of this study is to provide an evaluation of the health hazards and safety aspects of these smoke compounds.

Phosphorus exists in several allotropic forms of which the red and the white varieties are more common. Both the red and white forms produce a dense white smoke of phosphorus pentoxide upon burning. White phosphorus is preferred over red phosphorus as a smoke producing compound because on a quantity basis, the former produces more smoke and is considered the better smoke generator. There is a disadvantage of using white phosphorus as a smoke compound in that the smoke produced has a tendency to rise in a pillarlike mass, which frequently nullifies its screening effect, particularly in still air. This has been overcome to some extent by the development of plasticized white phosphorus and epoxy white phosphorus. Another smoke producing compound used by the military is butyl rubber/red phosphorus.

The present report provides available data on the toxicity, pharmacokinetics, sampling and analysis of red and white phosphorus. The toxicity of the plasticizer (styrene-butadiene rubber) and epoxy resin (Bisphenol A - epichlorohydrin) is also discussed under the sections on smoke compounds. Inhalation toxicity of the pyrolysis and combustion products of epoxy resin and the plasticizer are also briefly discussed. Sources examined to locate relevant information in the literature are included in the appendix. Also included in the appendix is a list of organizations contacted to obtain pertinent data on the phosphorus smoke compounds.

II. TECHNICAL SUMMARY

Several phosphorus smoke compounds, viz., white phosphorus, red phosphorus, butyl rubber/red phosphorus, plasticized white phosphorus, and epoxy white phosphorus have been used for generating screening smokes. Some of these compounds are also used in mortar shells, artillery shells, hand and rifle grenades, and compositions of signalling smokes.

Phosphorus exists in several allotropic forms of which the red and the white varieties are more common. Red phosphorus is thermodynamically more stable than the white phosphorus. White phosphorus ignites spontaneously in air while red phosphorus ignites only when heated to 260°C.

Plasticized white phosphorus and butyl rubber/red phosphorus are compounded by the treatment of red or white phosphorus with styrene-butadiene rubber (SBR) in a solvent like xylene or naptha. Epoxy white phosphorus is compounded by the treatment of white phosphorus with an epoxy resin (Bisphenol A-epichlorohydrin).

The data relating to toxicity and health hazards of plasticized white phosphorus, epoxy white phosphorus, butyl rubber/red phosphorus, and smoke generated from these compounds are not available in the literature. There is some information available relating to the acute effects of white phosphorus smoke on humans and animals. Limited studies have been carried out in animals on the inhalation toxicity of pyrolysis products of SBR and pyrolysis and combustion products of Bisphenol A-epichlorohydrin epoxy resin. The toxicological studies of red and white phosphorus, the inhalation toxicity of white phosphorus smoke and the inhalation toxicity of pyrolysis products of SBR and Bisphenol A-epichlorohydrin resin are summarized as follows.

A. TOXICITY OF RED PHOSPHORUS

No reference was found in the literature regarding the acute toxicity of red phosphorus in humans. There were some early reports of chronic effects due to the occupational exposure to red phosphorus, but these were inconclusive and of doubtful significance since the workers were also exposed to white phosphorus during their working hours.

Although it is claimed to be of low toxicity there are no significant studies available on the toxicological aspects of red phosphorus on experimental animals.

No studies have been reported in the literature to determine the potential carcinogenic, mutagenic and teratogenic effects of red phosphorus in humans or in animals.

No data are available on the absorption, distribution, metabolism and excretion of red phosphorus in humans. Only one report on the distribution studies in mice after inhalation of red phosphorus is available. In this study, radioactive red phosphorus was shown to be distributed in the digestive and respiratory tracts. After 2 days only the lungs showed some radioactivity.

No standards have been established for occupational exposure to red phosphorus.

B. HUMAN TOXICITY OF WHITE PHOSPHORUS

White phosphorus is one of the most highly toxic inorganic substances. It is a powerful systemic poison. The effects observed after acute and chronic intoxication are summarized as follows.

1. ACUTE EFFECTS

Acute intoxication has resulted generally after oral ingestion of roach poisons containing 1-4% white phosphorus. Contact with skin causes burns and inhalation of white phosphorus vapors has produced tracheobronchitis and liver enlargement.

ORAL INGESTION

The lethal dose of white phosphorus after oral ingestion in adult humans is about 60 mg, but as little as 15 mg may produce toxic symptoms. The initial symptom of intoxication is alliaceous or garlic-like taste developing a few hours after ingestion of the poison; this is followed by gastrointestinal irritation beginning with nausea, vomiting and gaseous eructations. The vomitus is black with the same characteristic garlic-like smell. Death may ensue in 12 hours from cardiovascular collapse and usually follows a period of delirium and coma. If death does not occur there is an apparent period of remission, and the patient appears cured. However, after 2 or 3 days the toxic symptoms reappear with intensified vomiting, melenous diarrhea, generalized abdominal pain, oliguria, hepatomegaly, gastrointestinal bleeding and fatty degeneration of liver and kidneys. Alcoholic beverages may tend to enhance absorption and may be more likely to end the acute toxic phase fatally.

SKIN CONTACT

Contact of skin with white phosphorus produces severe and painful burns, with destruction of the underlying tissues. Systemic effects observed include massive hemolysis, hematuria, hemoglobinuria and oliguria. A case of bone necrosis of the feet following white phosphorus burn has also been reported in the literature.

INHALATION

Acute phosphorus intoxication from inhalation has not often been reported. Recently, an instance has been reported where some workers were exposed to the vapors of both white phosphorus and phosphorus pentoxide at concentrations of 35 mg/m^3 and 220 mg/m^3, respectively, for 2-6 hours. The toxic symptoms observed were weakness, malaise, headache, vertigo, tracheobronchitis, and tender and enlarged livers.

2. CHRONIC EFFECTS

Chronic intoxication has been generally attributed to inhalation of white phosphorus vapors in industries, either manufacturing or using white phosphorus. Generally, chronic symptoms appear only after continued exposure for many years although as little as 7 weeks occupational exposure to white phosphorus fumes has also resulted in intoxication. Cases have also been reported among persons who ceased working in the phosphorus-contaminated atmosphere many years

before their symptoms appeared. No difference has been noted in the two sexes in susceptibility to white phosphorus intoxication. The age of the workers is of slight importance although persons under eighteen years may be more sensitive to white phosphorus intoxication.

The major characteristic of chronic white phosphorus toxicity is the involvement of bones, especially those of the jaw. In fact, the toxicity of white phosphorus after occupational exposure is well known as "phossy jaw" or necrosis of the jaw. The first change in the bones is a generalized hyperostosis. The process is first, a deposition of calcium salts, followed by a resorption of these salts, leading eventually to bone atrophy. As a result the bones become fragile, there is ossification of the growing centers and widened epiphyseal areas appear.

Another effect of chronic white phosphorus intoxication is on the blood picture. The level of potassium in the blood is decreased and those of chlorides and fat content are increased. In some cases leukopenia, anemia, and absence of methemoglobin have also been reported.

There are also some urinary changes associated with chronic poisoning, which include albuminuria, an increase in oxidized sulfur content, and an increase in levels of ammonia nitrogen at the expense of urea nitrogen.

Unlike acute white phosphorus intoxication, no effects on the liver and the central nervous system have been observed in chronic phosphorus intoxication.

The maximum allowable concentration in the United States in work areas for occupationally exposed personnel is 0.1 mg/m^3 (8-hour time-weighted average).

C. ANIMAL TOXICITY OF WHITE PHOSPHORUS

1. ACUTE EFFECTS

Reports of oral and subcutaneous administration, as well as inhalation are available. A summary of findings in the study of the acute toxicity of white phosphorus is presented in Table 13 on page 43.

ORAL ADMINISTRATION

The oral LD_{50} for rats and mice has been found to be 3.03-3.76 and 4.82-4.85 mg/kg body weight, respectively. The effects of these doses in both species were anorexia, and yellow and enlarged livers.

Rats fed 1.3 mg/kg body weight of white phosphorus for 16 days had wider metaphyseal tuberculae of proximal tibia and broadened metaphysis. A single dose of 10 mg/kg body weight of white phosphorus to rats by stomach tube caused fatty infiltration and degeneration of liver and biochemical changes in the liver.

INHALATION

The lowest published lethal concentration of white phosphorus vapors for mice has been reported to be 500 mg/m^3 (10 minutes).

Rabbits exposed to vapor concentrations of 150-160 mg/m^3 for half an hour daily for sixty days had a decrease in hemoglobin and erythrocyte counts.

SKIN CONTACT

A single application of a 0.1% solution (volume of application not specified) of white phosphorus in peanut oil did not cause any primary skin irritation in rabbits. A single application of 10 g white phosphorus into a 7.5 cm area of the back of rabbits caused deaths in 84 out of 130 animals within 3 days. The effects observed were decreased calcium and elevated phosphorus levels in the serum. White phosphorus applied as a 1.0% solution in peanut oil to the eyes of rabbits did not produce any irritation.

When 50 mg of white phosphorus was introduced into a 1.5 cm longitudinal incision made in the inguinal region of rats, the effects observed were 50% mortality, elevated levels of serum phosphate, serum glutamine-pyruvic transaminase, plasma potassium, and plasma urea nitrogen. The plasma sodium levels were lowered. Histopathologically there was extensive degeneration of hepatic cells. In the kidneys there was generalized swelling with desquamation, perinuclear vacuolization and necrosis of cells of the proximal tubules.

A dermal sensitization test in guinea pigs has not been reported.

SUBCUTANEOUS ADMINISTRATION

Dogs given a single injection of 0.1 mg/kg body weight subcutaneously developed hydropic degeneration of the kidneys and hemorrhagic livers. There was no significant fatty infiltration of the liver or kidneys. A single subcutaneous dose of 0.2 mg/kg body weight to dogs caused hemorrhage in the livers and kidneys. A single dose of 0.4 mg/kg body weight to dogs produced hematemesis, necrosis of the liver and fatty degeneration and extensive necrosis in renal tubules.

Subcutaneous administration of a single dose of 1.6-10 mg/kg body weight of white phosphorus to rabbits caused adrenal insufficiency and fatty infiltration in the liver.

When guinea pigs were given a single injection of 7.5 mg/kg body weight of white phosphorus in olive oil, the livers of animals were infiltrated with fatty deposits and consolidated with parenchymal necrosis and nuclear swelling.

2. CHRONIC EFFECTS

The chronic effects of white phosphorus in animals are summarized in Table 15 on page 48. The chronic intoxication in experimental animals has produced effects on growth, bones, liver, kidney, and the central nervous system, depending upon the route of administration. These effects are described as follows.

EFFECTS ON GROWTH

Oral doses of 0.0027-0.0032 mg/kg body weight daily for 22 weeks to rats produced a slight reduction in weight gain. Doses of 0.018-0.07 mg/kg body weight daily for 22 weeks to rats produced significant reduction in weight gain as compared to controls. Rats given 0.01% white phosphorus in the diet for 22-57 days showed reduction in weight gain. Likewise, rabbits given

oral doses of 0.3 mg/kg body weight per day of white phosphorus for 117 days showed an overall reduction in weight gain as compared to controls.

EFFECTS ON GROWING BONE

Oral administration of 0.3 mg/kg body weight of white phosphorus to rabbits daily for 117 days caused retardation of longitudinal bone growth. The epiphyseal plate was narrow and the diaphyseal marrow became less cellular as compared to the controls.

Rats receiving 0.01% white phosphorus in their diet for 57 days showed no effect on the bones. When rats were administered the same dose for 50 days, followed by 0.04% white phosphorus in diet from the 50th to 57th day, there was retardation of longitudinal bone growth, and the animals had a calciotraumatic line in the labial dentin.

Rats exposed to vapor concentrations of 150-160 mg/m^3 half an hour daily for sixty days had a widened epiphyseal line, irregularity of cell configuration, remarkable trabeculation associated with insufficient ossification and disordered axile development of long bones.

EFFECTS ON LIVER

Oral administration of white phosphorus to rabbits (3-14 drops of 1% and 3% solutions in oil daily) for 50 days produced an increase in the mitoses of fat storage cells in the sinusoid walls of the lobes of the liver. Kupffer cells showed an increase in the mitotic rate. There was morphological deformation of the mitochondria. The fatty infiltration was less, when compared to acute poisoning in these animals.

Rabbits and guinea pigs receiving white phosphorus in the diet at doses of 0.6-1 mg/kg body weight daily for more than 4 months (actual length of study not specified) had degenerative changes characteristic of hepatic cirrhosis. The hepatic changes were often complicated by ascites and jaundice. The effects were directed to stromal fibroblasts, particularly in the area of the portal vessels as well as parenchymal cells throughout the lobule. Dysfunction of cells was more massive when the dose administered was 1 mg/kg body weight/day, but decreased considerably when the dose was lowered to 0.33 mg/kg body weight. The shortest time to produce hepatic cirrhosis was 4 months.

Oral doses of 0.2-0.8 mg/kg body weight of white phosphorus daily for 37 days caused a decrease in plasma albumin and fibrinogen and an increase in globulin in dogs. There was evidence of degeneration of the liver parenchyma.

EFFECTS ON KIDNEYS AFTER SUBCUTANEOUS DOSES

Prolonged administration of 0.1 mg/kg body weight of white phosphorus in oil to dogs daily for 56 days caused hydropic degeneration in the kidneys. No other significant adverse effects were noted in the bones or liver.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

In rabbits receiving a 1% solution of white phosphorus in oil (type of oil not specified) (0.2-1.0 ml doses) intravenously twice or thrice a

week for 15 weeks, nerve degeneration in the central nervous system was noted. Prolonged administration of 0.04 mg/kg body weight of white phosphorus (route and length of study unspecified) to rats resulted in increased cortical excitability.

D. CARCINOGENICITY, MUTAGENICITY, AND TERATOGENICITY OF WHITE PHOSPHORUS

There are no reports of white phosphorus induced cancers in humans. In two animal experiments with white phosphorus, subcutaneous injections of 3.2 mg/kg of body weight, 2 times per week for over 610 days to rats, and of 1 mg/kg of body weight for over 55 days to dogs failed to cause tumors to develop.

There are no available studies concerning the possible mutagenic or teratogenic potential of white phosphorus in living systems.

E. PHARMACOKINETICS OF WHITE PHOSPHORUS

In humans and animals white phosphorus is absorbed through the skin, by ingestion, and through the respiratory tract.

In rats absorption was essentially completed in 24 hours (about 60-65% of the administered dose) when given a single oral dose of 0.3 mg/kg body weight of ^{32}P-labeled white phosphorus. The radioactivity was mainly distributed in the liver and skeletal muscle. The liver contained large amounts of radioactivity averaging 16% of the dose at 4 hours, 17% at one day, and 6% at 5 days. The amount in the muscle averaged 4%, 5.5%, and 6% at 4 hours, one day, and 5 days respectively. The radioactivity in the blood represented 6%, 4%, and 2% of the administered dose and the end of 4 hours, one day, and 5 days, respectively. The amount of radioactivity remaining in the gastrointestinal tract was 57%, 15%, and 2% of the administered dose at the end of 4 hours, one day, and 5 days, respectively. The distribution of radioactivity in the various tissues, relative to plasma, 4 hours after administration of the label was in the following order: liver > kidneys > lungs > spleen > bone > muscle > brain.

White phosphorus is metabolized in the body (humans and animals) to phosphate, although the site or sites of this oxidation has not been studied. The urinary metabolites include organic and inorganic phosphates.

In humans and in rats the metabolites of white phosphorus are excreted chiefly in the urine. Insignificant amounts of unchanged white phosphorus may be excreted in the exhaled breath, sweat, and feces.

F. INHALATION TOXICITY OF WHITE PHOSPHORUS SMOKE

1. HUMANS

The smoke produced after burning white phosphorus in air contains mainly phosphorus pentoxide which in the presence of moisture is converted to phosphoric acid. A concentration of 1000 mg/m^3 in air of white phosphorus smoke (composition of the smoke not given) is intolerable to human subjects. The minimum harassing concentration of white phosphorus smoke is about 700 mg/m^3. Respiratory distress, nasal discharge, coughing and soreness

and irritation of throat were noted in subjects exposed to about 600 mg/m^3 for 2-4 minutes. Irritation of nose and throat and coughing were observed in men exposed to levels of up to 500 mg/m^3 for 16 minutes. The symptoms disappeared in all the cases three days post exposure.

The Occupational Safety and Health Administration (OSHA) of the United States Department of Labor has set the limiting concentration of phosphoric acid as 1.0 mg/m^3 for occupational exposure (8-hour time-weighted average). No standards have been set for phosphorus pentoxide but a threshold limiting value of 1.0 mg/m^3 has been recommended for occupational exposure by the American Industrial Hygiene Association.

2. ANIMALS

When mice were exposed to white phosphorus smoke at a concentration of 110-900 mg/m^3 for one hour, there were no deaths during the exposure, but about 20% of the animals died 24 hours - 10 days later. At concentrations of 1230 mg/m^3 five out of 20 animals died during a one-hour exposure, while at 1690 mg/m^3 fourteen out of 20 animals died during the exposure. Death in all cases was due to respiratory failure. Other effects observed were hemorrhagic lungs and occasional cloudy swelling of heart, liver and kidney cells.

Exposure of ten rats to concentrations up to 4800 mg/m^3 caused one death during one hour exposure at 4530 mg/m^3, and one death occurred 24-48 hours after a one hour exposure to 1350 mg/m^3. At concentrations of 4460-4810 mg/m^3 for one hour all the rats died 1-10 days post exposure. Autopsy findings included pulmonary congestion, edema, occasional atelectasis and cloudy swelling of hepatic and renal cells.

White phosphorus smoke at levels ranging from 540-4810 mg/m^3 for one hour did not cause any deaths in goats up to 10 days post exposure. At concentrations ranging from 5230-7310 mg/m^3 about 3-6 out of 10 goats died 5-10 days post exposure. There were some deaths in the animals 24 hours post exposure when the concentration was increased to 7750-11470 mg/m^3 for a one hour exposure. Autopsy findings were pulmonary edema, atelectasis and pneumonia, cloudy cell swelling and congestion of the liver and kidneys.

G. TOXICITY OF BUTYL RUBBER/RED PHOSPHORUS AND PLASTICIZED WHITE PHOSPHORUS SMOKE COMPOUNDS

There are no data available in the literature relating to the toxicity of butyl rubber/red phosphorus or plasticized white phosphorus in humans or in animals. Red phosphorus appears to be non-toxic but has been little studied, and the toxicity of the white phosphorus has been summarized in the preceding sections.

In one study on the plasticizer (styrene-butadiene rubber) mice were exposed to the pyrolysis products of one gram of styrene-butadiene rubber in a 4.2 liter chamber. The mice staggered after 11 minutes, convulsed, and collapsed after 20 minutes, and died after 23 minutes. The pyrolysis products in the chamber were found to be oxygen, carbon dioxide, carbon monoxide, methane, and ethylene. The cause of death was carboxyhemoglobinemia resulting from exposure to carbon monoxide.

It should be emphasized, however, that the levels of these gases would be different when butyl rubber/red phosphorus or plasticized white phosphorus is burned in air since the excess of atmospheric oxygen will convert carbon monoxide to carbon dioxide.

No studies are available on mutagenicity, teratogenicity, or carcinogenicity of butyl rubber/red phosphorus or the plasticized white phosphorus smoke compounds.

H. TOXICITY OF EPOXY WHITE PHOSPHORUS SMOKE COMPOUND

There are no studies available relating to the toxicity of epoxy white phosphorus in humans or in animals. The toxicity of white phosphorus has been summarized in the preceding sections.

The epoxy resin (Bisphenol A-epichlorohydrin) used for formulating epoxy white phosphorus is a mild skin sensitizer in humans.

No effects were observed in rats exposed to the combustion products of the epoxy resin (20 g of the resin burned) in a 300 liter chamber for one hour.

Pyrolysis products of the epoxy resin under the aforementioned conditions, using a 1.0 g sample, had no effects in rats. When the weight of the epoxy resin pyrolysed was in the range of 1.4-16.0 g, deaths occurred among the rats, the number depending upon the weight of the sample. The principal cause of death was respiratory failure from pulmonary edema.

Bisphenol A-epichlorohydrin resin was not found to be carcinogenic in mice.

There are no data available on the mutagenicity, carcinogenicity or teratogenicity of epoxy white phosphorus smoke compound.

III. RECOMMENDATIONS FOR FUTURE EXPERIMENTAL STUDIES ON PHOSPHORUS SMOKE COMPOUNDS

At the present time, there is no information available on the toxicological aspects and health hazards of the three phosphorus smoke compounds, viz., butyl rubber/red phosphorus, plasticized white phosphorus and epoxy white phosphorus. The chemical composition of the smoke generated from these compounds is also unknown. Following are some recommendations for future experimental studies on the phosphorus smoke compounds, and including white phosphorus and red phosphorus.

1. ANALYSIS OF SMOKE

Before inhalation experiments are conducted on phosphorus smoke produced by the three smoke compounds, it will be important to determine concentrations encountered in field use.

As part of this determination an analysis of the components of the smokes, and their relative concentration ought to be undertaken. Phosphorus smoke has been reported to consist mainly of phosphorus pentoxide and/or phosphoric acid. However, the conditions of generation of the smokes, and the use of plasticizer and epoxy resin may alter their composition. Of particular importance is the presence of any uncombusted phosphorus in the form of dust or vapor.

2. TOXICOLOGICAL TESTING OF RED PHOSPHORUS

Although red phosphorus has been considered to be relatively nontoxic, there is relatively little scientific basis for this judgement. Appropriate toxicological testing is required; Table 1 summarizes areas where adequate data are lacking.

3. TOXICITY OF SMOKE AGENTS

There are no data available on the toxicity and metabolic fate of any of the three subject smoke compounds (see Table 1). These should be undertaken in light of possible exposure to those manufacturing and using these compounds. However, white phosphorus is the major constituent of two of these compounds (plasticized white phosphorus and epoxy white phosphorus), and sufficient information has accrued on the danger of this allotrope to warrant institution of adequate occupational safety and health practices.

4. INHALATION EXPERIMENTS ON SMOKE

Acute and chronic studies of inhalation effects of the smokes produced from plasticized white phosphorus, butyl rubber/red phosphorus, epoxy white phosphorus and red and white phosphorus have not been conducted to date, as seen in Table 1. It is recommended that such studies be undertaken in appropriate experimental animals.

Specific kinds of toxicological studies which have not been adequately performed for red phosphorus, white phosphorus and smoke compounds are detailed in Table 1. An examination of this table will provide an indication of the types of studies which will prove beneficial for a final evaluation of the health hazards of these compounds.

TABLE 1

GAPS IN TOXICOLOGICAL STUDIES

Compounds:	Red Phosphorus	White Phosphorus	PRP	PWP	EWP	butyl rubber/ P Smoke	PWP Smoke	EWP Smoke	Red and White Phosphorus Smoke
PHASE I:									
Acute Oral LD_{50}	X		X	X	X				
Acute dermal LD_{50}	X		X	X	X				
Acute inhalation LC_{50}						X	X	X	X
Eye and skin irritation	X	X	X	X	X	X	X	X	X
Skin sensitization	X	X	X	X	X	X	X	X	X
Metabolism in various animals[a]	X		X	X	X	X	X	X	X
Mutagenesis in microbes[b]	X	X	X	X	X	X	X	X	X
PHASE II:									
14-Day feeding	X		X	X	X				
90-Day feeding	X		X	X	X				
Subacute inhalation studies						X	X	X	X
PHASE III:									
2-Year feeding[c]	X	X	X	X	X				
180-Day feeding	X	X	X	X	X				
Chronic inhalation studies						X	X	X	X
Fertility, reproduction	X	X	X	X	X	X	X	X	X
Teratology	X	X	X	X	X	X	X	X	X
Metabolism in various animals[d]	X		X	X	X	X	X	X	X

a. Metabolism will include absorption, distribution, excretion, and pharmacokinetics, using radio-labeled material.
b. Ames test, including activation.
c. This will include a carcinogenicity evaluation.
d. This will include the identification and possible isolation of any metabolites.

PWP- plasticized white phosphorus
EWP- epoxy white phosphorus
X- marks indicate that an adequate study has not been undertaken

IV. CHEMISTRY OF PHOSPHORUS

Although an Arabian alchemist named Alchid Bechil probably discovered phosphorus as early as the twelfth century, the discovery of the element is usually attributed to Hennig Brandt, in 1669, who was said to be an impoverished merchant seeking to restore his wealth by converting base metals into gold. The name phosphorus, meaning light-bearer, was first applied to all substances which glowed in the dark, but was later restricted to this element, which originally bore such names as phosphorus mirabilis and noctiluca consistens (1). Atomic number, atomic weight and other related data about this element are provided in Table 2.

TABLE 2

NOMENCLATURE AND RELATED DATA

Chemical Name:	Phosphorus
Symbol:	P
Chemical Abstract Service (CAS) Registry Number:	007723140
Wiswesser Line Notation (WLN):	P
Atomic Number:	15
Atomic Weight:	30.98
Molecular Formula:	P_4
Molecular Weight:	123.92

ALLOTROPES OF PHOSPHORUS

Elemental phosphorus exists in several allotropic forms. The best known variety is white phosphorus (sometimes called yellow or elemental phosphorus), which is the form of greatest commercial importance. The other class of solid allotropes having some commercial importance is red phosphorus. The third variety is black phosphorus which is uncommon and has no commercial value. Only the white and red forms of phosphorus have been included in the present study.

WHITE PHOSPHORUS

The most common form of phosphorus is α-white phosphorus, a solid obtained by the condensation of phosphorus vapor to a liquid and then allowing the latter to solidify under water. White phosphorus, when pure, is a colorless waxy solid melting at 44.1°C to a clear liquid. Commercial white phosphorus is 99.9% pure, with the major impurities being arsenic (usually under 0.02%), and traces of hydrocarbons (1,2). It has a slight yellow color and melts to a straw-colored liquid. Presumably the yellow color is due to traces of red phosphorus (3). The α-white phosphorus crystallizes from solution when dissolved in carbon disulfide, or by cooling the vapor. The x-ray diffraction shows that the α-white phosphorus is cubic with large unit cells containing 56 molecules of P_4 and a lattice constant of 7.17 Å. It is a non-conductor of electricity (2). The physical properties and physical constants of α-white phosphorus are summarized in Table 3.

TABLE 3

PHYSICAL PROPERTIES OF α-WHITE PHOSPHORUS *

Appearance:	colorless to yellow, waxy solid		
Melting point:	44.1°C		
Boiling point:	280.5°C		
Crystal structure:	cubic		
Density:	1.828 g/cm^3		
Autoignition temperature:	30°C in moist air, higher in dry air		
Critical temperature:	695°C		
Critical pressure:	82.2 atmospheres		
Index of refraction:	1.8244 for D line at 29.2°C		
Heat of fusion:	600 ± 3 cal/mole P_4 at 317.26°K		
Heat capacity:	at 25°C = 22.18 cal/mole/degree		
	at 44.1°C = 22.73 cal/mole/degree		
Sublimation pressure (mm):	0.025 (at 20°C), 0.043 (at 25°C),		
	0.072 (at 30°C), 0.089 (at 35°C),		
	0.122 (at 40°C)		
Vapor pressure:	1 mm Hg at 76.6°C		
Heat of sublimation:	13.4 Kcal/mole P_4		
Heat of combustion:	710.2 ± 1.0 Kcal/mole P_4		
Solubility:	Cold water	:	Almost insoluble
	Hot water	:	Slightly soluble
	Absolute alcohol	:	2.5 g/l
	Ether	:	10 g/l
	Chloroform	:	25 g/l
	Benzene	:	28.5 g/l
	Carbon disulfide	:	1250 g/l

* From references 1,2,3,4.

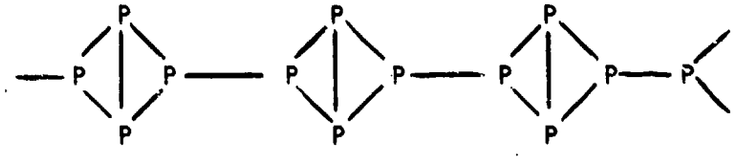
When α-white phosphorus is cooled below -76.9°C at atmospheric pressure, a hexagonal modification is formed. This material, which has the same general appearance and characteristics as the α-form, is called β-white phosphorus. The heat of transformation of the α- to β-form is equal to -3.8 ± 0.2 Kcal/mole P_4 at -76.9°C (2).

RED PHOSPHORUS

Commercial red phosphorus is prepared by heating white phosphorus at about 400°C for several hours. Iodine, sulfur or sodium may be used as a catalyst. Red phosphorus as prepared by commercial processes is almost entirely amorphous (1,2). Red phosphorus prepared by various methods exhibits different properties. The melting point is reported to range from 585-600°C; and measured densities have been found to vary between 2.0 and 2.4 g/cm^3; the color of red phosphorus is found to vary from a deep scarlet to brown, and to violet, depending on the method of preparation. As many as six modifications of red phosphorus may exist but not all of them are structurally characterized.

The physical properties of red phosphorus are presented in Table 4.

The structure of red phosphorus may be the result of cleavage of one of the P_4 tetrahedron bonds followed by polymerization into the following molecular chain.



The conditions of formation, chain structures of variable length and different terminal groups, which are always impurities (such as the catalysts used, or O and OH groups from stray oxygen or water and other impurities) probably account for variety in the forms and properties of red phosphorus (2). Amorphous red phosphorus is also formed by ultraviolet irradiation of white phosphorus in various solvents in which case red phosphorus incorporates within it small amounts of impurities derived from the solvent. In the case of organic halides as solvents, the organic radical appears to be strongly bound to the phosphorus, since it cannot be removed by boiling with water, and oxidation of the phosphorus with nitric acid yields the corresponding alkyl or aryl phosphinic acids (1).

A thermal analysis of the process occurring when amorphous red phosphorus is heated shows the presence of various modifications of red phosphorus (1). Red phosphorus-I is the original amorphous material, which transforms to red phosphorus-II at 460°C. The second transformation corresponds to red phosphorus-II going to red phosphorus-III at 520°C, and the transformation from red phosphorus-III to red phosphorus-IV occurs at 540°C. The x-ray pattern of Forms-II and -III are quite similar, and it is suggested that, indeed, Forms-II and -III may even be poorly crystallized varieties of Form-IV. Microscopic examination of

TABLE 4

PHYSICAL PROPERTIES OF RED PHOSPHORUS *

Appearance:	Reddish-brown amorphous powder (commercial)
Melting point (triple point):	590°C at 43.1 atmosphere
Boiling point:	280°C
Ignition temperature:	260°C
Density:	2.31 g/cm^3
Heat of sublimation:	19.7 - 28.8 Kcal/mole P_4
Heat of combustion (amorphous) :	703.2 ± 0.5 Kcal/mole P_4
(crystalline) :	697.7 ± 0.4 Kcal/mole P_4
Solubility:	Very slightly soluble in cold water, insoluble in organic solvents, soluble in phosphorus tribromide.

* From references 1,2,4,5.

the crystals has shown that Form-IV is tetragonal and Forms-II and/or -III may be hexagonal. The transitions found by thermal analysis are not reversible (1).

Form-IV of red phosphorus is definitely well crystallized. It is produced as well-formed crystals by slow condensation of phosphorus vapor at 425°C. It can also be made in a microcrystalline form by allowing molten phosphorus at about 600°C to cool and then holding it at a temperature around 550°C for crystallization (1).

The crystalline modification of red phosphorus which has been best defined is the triclinic variety also called red phosphorus-V, violet phosphorus, metallic phosphorus or Hittorf's phosphorus. This is prepared by slow condensation (up to 30 days) from the phosphorus vapor at 550°C on a surface maintained at 545°C. It can also be made by heating amorphous red phosphorus at 550°C for several weeks (1).

A cubic form of red phosphorus has also been reported which is made by heating white phosphorus at temperatures near 600°C (1).

The deep red form of phosphorus is made by subjecting white phosphorus to a pressure of 8000 atm at 300°C, and is denoted as red phosphorus-VI (1).

STABILITY AND INTERCONVERSION OF RED AND WHITE PHOSPHORUS

Red and white phosphorus show a difference in reactivity. White phosphorus is by far the most reactive form and red phosphorus is relatively less reactive. White phosphorus must be stored under water to protect it from air, whereas red phosphorus is stable in air. White phosphorus ignites in air spontaneously and red phosphorus ignites only when heated in air at 260°C. Heating white phosphorus between 400-600°C produces red phosphorus. The same liquid is obtained no matter whether white or red phosphorus is melted or the vapor is condensed. On rapid cooling, white phosphorus is obtained (1,2). Red phosphorus is thermodynamically more stable than white phosphorus. The free energy of formation ΔF, for red phosphorus is -3.3 Kcal/mole and for white phosphorus it is 0.0 Kcal/mole (1).

LIQUID PHOSPHORUS AND PHOSPHORUS VAPOR

The same liquid is obtained no matter whether white, red or black phosphorus is melted or the vapor is condensed. Upon cooling the liquid phosphorus obtained by melting any of the solid modifications, white phosphorus is formed (1,2). The vapor pressure curves of liquid white and red phosphorus appear to be different sections of the same line as illustrated by Figure 1. Because of the rapid formation of red phosphorus, the liquid does not exist in the region represented by the broken portion of the line in Figure 1 (1).

Liquid phosphorus is very easily supercooled, and droplets of 1.0 mm or less have been cooled to -71.3°C, which is 115.4°C below the melting point of white phosphorus. The crystallization of supercooled phosphorus is extremely rapid. X-ray diffraction study of liquid phosphorus indicate that the phosphorus atoms are present in the form of symmetrical P_4 tetrahedra with a P-P distance of 2.25 Å (1).

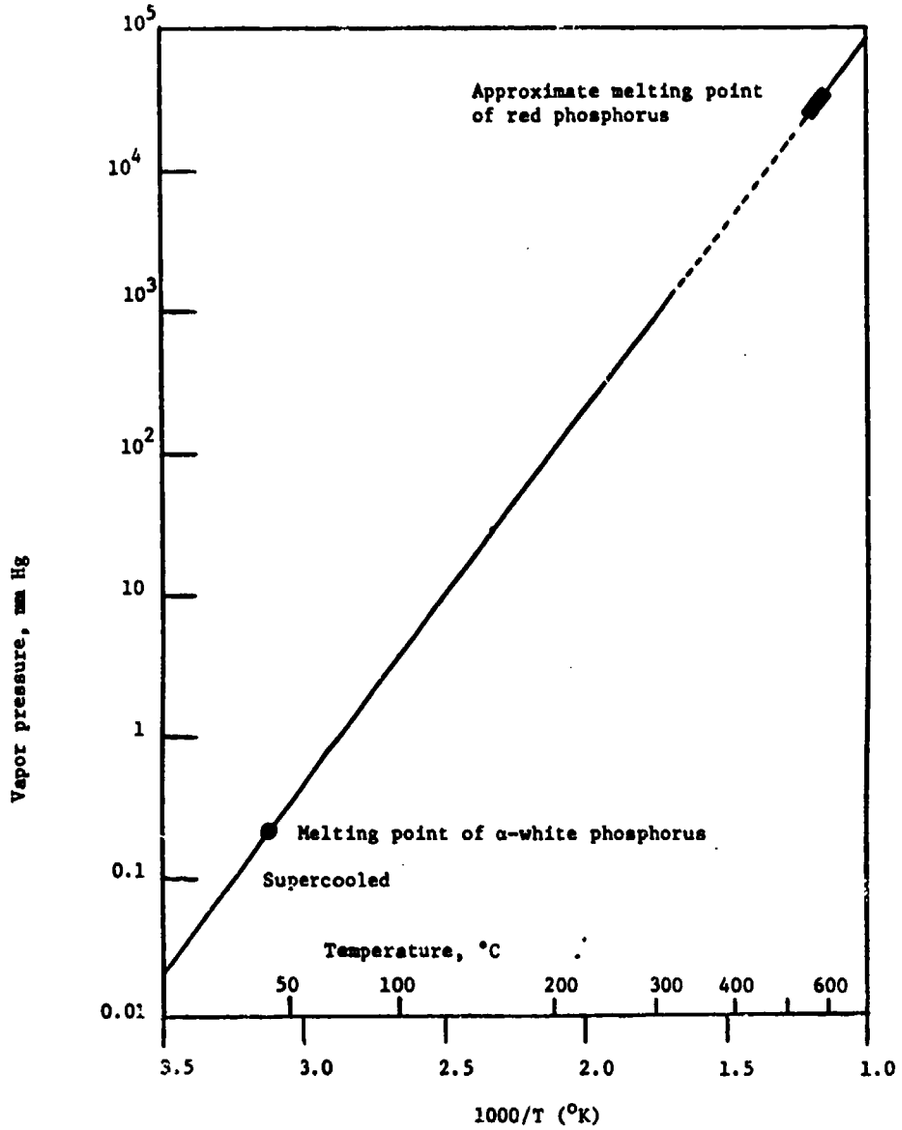


Figure 1. Vapor pressure of liquid phosphorus. Because of the rapid formation of red phosphorus, the liquid does not exist in the region represented by the broken portion of the line (1). The values of vapor pressure were calculated by the following equations.

$$\log p_{mm} = 18.8192 + 1.074 \times 10^{3}\ T - 3.096 \log T - 3.2167 \times 10^{3}\ T^{-1}$$

(for temperatures between 45-350°C)

$$\log p_{mm} = -2196.01/T + 7.0663$$ (for temperatures between 510-630°C)

(Ref: T.D. Farr, Tennessee Valley Authority Chem. Eng. Report No. 8, 2-17, 1950)

At temperatures below 800°C phosphorus vapors contain tetrahedral P_4 molecules. At higher temperatures there is considerable dissociation of P_4 molecules to P_2 molecules. For the range from 900-1200°C the following equation gives the ratio of the pressures in atmospheres (p_2 and p_4), of the diatomic and tetratomic molecules, respectively, as a function of absolute temperature, T (1):

$$\log (p_2^2/p_4) = 7.5787 - (11489/T)$$

CHEMICAL PROPERTIES OF RED AND WHITE PHOSPHORUS

In general, the reactions of red and white phosphorus are similar. White phosphorus is considerably more reactive than the red phosphorus. White phosphorus ignites spontaneously in air while red phosphorus is much more stable. At normal temperatures and humidities, red phosphorus reacts slowly with the water vapor and oxygen in air to form phosphine and a mixture of oxyacids of phosphorus. This slow oxidation is exothermic and is accelerated by an increase in temperature, so that spontaneous combustion may result if large quantities of red phosphorus are stored in piles. Traces of copper, iron, silver, nickel and bismuth catalyze the oxidation of red phosphorus by moist air. Since iron and copper are usually present in commercial red phosphorus in concentrations of about 0.025% and 0.003%, respectively, removal of these metals will noticeably increase the stability of the red phosphorus. Moreover, addition of certain substances, such as hydrated aluminum oxide, is found to inhibit the oxidation (1).

Under most conditions both red and white forms of phosphorus react with atmospheric oxygen to give phosphorus pentoxide as the major product which is then converted by the moisture in air to phosphoric acid (6). Both red and white phosphorus react with aqueous alkali to give phosphine; combine with halogens to give tri-or pentahalides; reaction with sulfur produces sulfides; and the reaction with metals and non-metals produces phosphides (7).

COMBUSTION OF PHOSPHORUS AND GENERATION OF SMOKE

Combustion of white phosphorus in air produces a dense white smoke of phosphorus pentoxide (P_4O_{10}) which in the presence of moisture is then converted to phosphoric acid (3). In World War II, white phosphorus was used both as a screening smoke and an incendiary in all theaters of operations (8). Since white phosphorus has a high heat of combustion (710 Kcal/mole), the smoke produced by it has a tendency to rise in a pillar like mass, which frequently nullifies its screening effect, particularly in still air (9). There are several major disadvantages of using white phosphorus as a smoke generating agent. Its storage and handling are difficult and require special equipment, due to its spontaneous flammability. Its melting point is below temperatures frequently encountered in storage. It produces a bright flame while burning and being a solid it cannot be sprayed without dissolving in highly flammable and dangerous solvents (6,10).

$$4P + 5\ O_2 \longrightarrow P_4O_{10}$$
$$P_4O_{10} + 6H_2O \longrightarrow 4H_3PO_4$$

Red phosphorus upon burning also generates a smoke of phosphorus pentoxide which in the presence of moisture is converted to phosphoric acid. Red phos-

phorus does not ignite below 260°C while white phosphorus ignites spontaneously in air (6).

Although white phosphorus has some disadvantages, it is preferred over red phosphorus as a smoke producing compound because on quantity basis, the former produces more smoke and is considered the better smoke generator (6).

V. HUMAN TOXICITY OF RED PHOSPHORUS

Reports of adverse health effects of red phosphorus are not available. Early reports of chronic effects due to occupational exposure which are inconclusive and of doubtful significance are described below.

A. ACUTE EFFECTS

There is no information available in the literature regarding the acute toxic effects of red phosphorus in humans.

B. CHRONIC EFFECTS

Heimann (11) presented a case of chronic phosphorus intoxication which, though attributed to the red allotrope, is dubious because of the circumstances of the patient's work.

A 40 year old man worked for eight years in a plant which converted white phosphorus into red phosphorus. Periodic medical and dental examinations were normal. While on vacation from work some teeth were extracted because he complained of joint pains. Since the pain did not subside, he returned to the hospital where osteomyelitis of the left mandible was diagnosed with eventual surgical removal of a portion of the left mandible (11). The toxicity was not attributed solely to red phosphorus but due to the fact that during the manufacture of red phosphorus from white phosphorus some of the white phosphorus remains unconverted. This unconverted white phosphorus could be the etiologic cause of the bone pathology (11).

C. EPIDEMIOLOGY

No information is available in the literature on the epidemiology of red phosphorus.

VI. ANIMAL TOXICITY OF RED PHOSPHORUS

The nature of red phosphorus toxicity has been somewhat clarified by animal experimentation.

A. ACUTE EFFECTS

Ferrannini (12) reported an experimental study in which a single dose of 100 mg/kg body weight of red phosphorus was injected into the jugular vein of rabbits (number of rabbits not indicated). After three days, the rabbits lost appetite and all died within six to eight days. Postmortem examination of the rabbits revealed extensive fatty degeneration of the liver and kidneys. Hematological assessment revealed leukopenia and a decrease in the red blood cell count. Other pathological findings were splenic and genital hyperplasia as well as nerve tissue degeneration.

B. CHRONIC EFFECTS

Ferrannini (12) reported an animal study of chronic toxicity (dose and species not indicated) whose results included acute parenchymatous

or interstitial nephritis. Other chronic toxic effects noted were induction of alopecia and desquamation of the skin. This study, however, offers inadequate information to enable proper evaluation because neither the dose of red phosphorus, the length of experimental period nor the species of animals was given.

VII. CARCINOGENICITY, MUTAGENICITY, TERATOGENICITY OF RED PHOSPHORUS

No studies have been reported in the literature to determine potential carcinogenic, mutagenic or teratogenic effects of red phosphorus.

VIII. PHARMACOKINETICS OF RED PHOSPHORUS

The deposition and retention of a ^{32}P-labelled red phosphorus aerosol with a mean particle diameter of 0.46 microns were studied in 15 mice (sex, age, not given) (13). The mice were exposed to a concentration of 5 mg/m^3 in an inhalation chamber for one hour. They were then sacrificed in 5 groups of 3 mice per group at the following times after exposure ended:

1st group	:	immediately
2nd group	:	20 minutes
3rd group	:	2 hours
4th group	:	48 hours
5th group	:	10 days

Autoradiographic scanning of whole-sectioned mice indicated high radioactivity in the digestive and respiratory tracts immediately after exposure to the red phosphorus aerosol. At 20 minutes and 2 hours post-exposure, activity was no longer detected in the upper respiratory tract. After 2 days and 10 days only the lungs showed some radioactivity (13). Metabolism was not discussed.

No information is available on the absorption, distribution, metabolism or excretion of red phosphorus in humans.

IX. INDUSTRIAL HYGIENE AND SAFETY PRACTICES FOR RED PHOSPHORUS

Red phosphorus must be stored in a cool place away from oxidizing agents. It is not spontaneously inflammable but its handling is hazardous since it may be ignited by friction, static electric discharge, heating and mixing with strong oxidizing agents. Users of red phosphorus are consequently to be aware of the fire hazard which may be minimized by using phosphor-bronze or copper tools as well as grounding of plant and equipment.

Blanketting the Red Phosphorus with nitrogen or handling it in aqueous solution helps to prevent fires. Should fires result, they may be controlled by covering with water applied as a low pressure spray or with nitrogen. A build-up of dust suspension in the air should be avoided especially in enclosed areas since dust explosions can occur upon ignition. It is advisable to keep plant and equipment permanently wet to avoid fires if deposition of red phosphorus on them is inevitable. Accumulation of the dust can also be prevented by frequently washing working areas. Such areas should be devoid of hot surfaces or flames. Face masks ought to be worn to prevent dust inhalation and clothing should be regularly washed. Some of the recommended protective clothing include hair-covering, armlets, polyvinyl chloride (PVC) gloves and PVC aprons or overalls;

shoes should be covered by spats. In the event of accidental abrasion to the skin or eyes, copious amounts of water should be used to wash while immediate medical attention is sought (14).

X. STANDARDS FOR RED PHOSPHORUS

No standards have been established for red phosphorus dust in the air. There is no threshold limit value (TLV) available.

XI. HUMAN TOXICITY OF WHITE PHOSPHORUS

White phosphorus is a highly toxic substance. The toxic effects are probably due to disturbance of intracellular oxidation processes caused by its potent reducing properties (15). Following is a review of acute and chronic toxicity of white phosphorus to humans. The toxicity discussed in this section includes effects after oral ingestion, inhalation of phosphorus vapors, and skin contact. The effects observed after inhalation of phosphorus smoke (which mainly consists of phosphorus pentoxide) are discussed in a separate section on Inhalation Toxicity of Phosphorus Smoke.

A. ACUTE EFFECTS

Acute, fatal intoxication caused by ingestion of yellow phosphorus was once common but has rarely been observed in recent years. At present, most acute white phosphorus intoxications result from ingestion of rat or roach poisons containing 1-4% white phosphorus as the active ingredient (16). Effects after skin contact and after inhalation are also discussed.

1. ORAL INGESTION

The lethal dose of white phosphorus after oral ingestion in adult humans is about 60 mg (1 mg/kg body weight) and as little as 15 mg (0.2 mg/kg body weight) may lead to untoward symptoms (17).

Acute phosphorus toxicity after oral ingestion of toxic doses follows a two-stage pattern (17). There is an initial stage of gastrointestinal irritation which begins with nausea, vomiting and gaseous eructations. This could start barely 30 minutes after ingestion of the poison. Death can result in about 12 hours from cardiovascular collapse. If this latter event does not occur, there is an apparent period of remission lasting about 48 hours during which patients are almost symptom-free. The return of symptoms during the second stage takes on a more severe form as exemplified by the following case histories.

A 31 year old housewife ingested about 8 g of rat poison containing 0.19 g white phosphorus (equivalent to 2.7 mg/kg body weight; other components of the poison were not specified). In spite of severe epigastric pain, nausea and vomiting, she refused all emergency treatment. Her symptoms abated on the second day but she still complained of intermittent epigastric distress. Her condition worsened from the fourth day onwards with intesified vomiting, melenous diarrhea, generalized abdominal pain, oliguria, hepatomegaly and pitting edema of the ankles. There were signs of gastrointestinal bleeding and she died. The autopsy revealed fatty infiltration of the liver and kidneys (17).

The usefulness of gastric lavage in the treatment of white phosphorus intoxication is exemplified in the case of a 19-year old male who was admitted into the hospital 5 1/2 hours after he ingested 11.1 mg/kg body weight of white phosphorus in half a tube of rat exterminator mixed with a half pint of lysol. The patient began vomiting 2 hours after ingesting the poison. He was dizzy, weak and had severe abdominal pain as well as burning in the

throat. He received stomach lavage promptly with copious amounts of 0.1% aqueous solution of potassium permanganate. Two days after admission the liver was enlarged and tender and on the third day he was jaundiced. Treatment consisted of daily intravenous infusions of 5% glucose in saline (3,000 mg), 1 ml of vitamin B complex (mg concentration not indicated) and daily intramuscular injections of liver extract (5 units). The patient recovered. It was suggested that gastric lavage is a life-saving procedure if it is performed within 5 hours after ingestion of the poison (17).

The rapidity of onset of acute effects depends upon the rate of absorption of the poison; this is influenced by the quantity ingested as well as by the vehicle used with the ingestion. Alcoholic beverages may tend to enhance absorption and may be more likely to end the acute toxic phase fatally; see Table 5 (17).

TABLE 5

NATURE OF VEHICLE AS A FUNCTION OF THE MORTALITY RATE

Vehicle	Cases	Deaths	Mortality %
Water	18	10	56
Rum	9	8	89
None	10	3	30
Unknown	5	1	20
Coffee	4	0	-
Beer	3	3	100
Malt Beverage	2	0	-
Wine	1	1	100
Milk	1	1	100
Bread & Crackers	2	0	-
Lysol	1	0	-

Ref: Diaz-Rivera (17).

The most common pathological findings in deaths due to acute phosphorus toxicity have been the fatty degeneration of liver and kidneys. However, Talley (18) reported a fatal case of phosphorus intoxication in which cardiovascular collapse was the cause of death. A 16-year old girl ingested 15.7 mg/kg body weight of white phosphorus in a suicide attempt. Upon admission to the hospital her pulse was 110/minute with a systolic pressure of 60 mm Hg, she was cyanotic and manifested poor capillary filling. The electrocardiogram (EKG) revealed atrial fibrillation with wide slurred QRS complexes and a supine chest x-ray showed diffuse cardiac enlargement. Twenty-two hours after ingesting the poison she died of cardiac arrest. Post-mortem examination showed a pale, dilated heart. Histologically, there were diffuse changes in the myocardium whose cells were separated by interstitial edema without cellular infiltrate. The cytoplasm was vacuolated with pale linear areas (18).

Hematological abberations resulting from acute phosphorus poisoning have been reported in a case by Newburger et al. (19). The observation was made in a 21-year old soldier who recovered after ingesting 21.4 mg/kg body weight of white phosphorus (60 g of rat poison 2.5% of which was white phosphorus; other components of the poison were not listed). There was definite leukopenia and neutropenia. However, others believe that the changes in the blood picture, with the exception of the blood-chemistry abberations of hyperphosphatemia and hypocalcemia, are too general and uncharacteristic and may not necessarily indicate phosphorus poisoning (20).

Early vomiting could have a protective effect by greatly reducing absorption and hence mortality. Of 17 individuals who vomited within one hour after ingesting phosphorus 7 died (42%) as opposed to 8 deaths (57%) from a group of 14 who vomitted between 2 to 7 hours after ingestion. There was a mortality rate of 80% in the group that did not vomit at all (17). It ought to be stated, however, that these figures cannot be properly evaluated statistically because it is presumed that not all the probands ingested the same amount of the poison, nor is there any distinction made in the sex and age differences, as well as the state of stomach and its contents (see Table 6).

TABLE 6

INFLUENCE OF EARLY VOMITING ON MORTALITY RATE

Hours after Ingestion	Cases	Deaths	Mortality %
0-1/2	19	6	32
1/2-1	8	1	13
1-2	6	3	50
2-3	6	4	67
4	1	0	-
7	1	1	100
No Vomiting	14	11	80
Time Unknown	1	1	100
Total	56	27	48

Ref: Diaz-Rivera (17).

2. WHITE PHOSPHORUS BURNS (Skin Contact)

Severe and painful skin burns occur when any part of the body is brought into direct contact with white phosphorus. Such burns are known to have

deeper underlying tissue destruction and are to be treated promptly and efficiently so as to minimize deeper penetration of the phosphorus (21). Usually the affected area turns grayish white and sepsis invariably sets in (20).

Summerlin (22) reported a case of massive hemolysis following white phosphorus burns. A 25-year old man was admitted with 29% of his body burned when an enemy white phosphorus grenade exploded at his feet in Vietnam. The wounds were debrided and cleansed and 2% copper sulfate solution was applied within 15 minutes of the accident. Twenty-three hours later his urine turned dark but the hourly urine volume output was not affected. The sclerae became icteric 36-hours after the accident and later the hematocrit dropped from 18 to 11% and the hemoglobin from 7.9 to 4.1 g/100 ml. Fresh urine hemoglobin was 4.9 g/100 ml and the urine supernatant hemoglobin was 4.7 g/100 ml. The urine had only an occasional red cell and there were no hemoglobin casts. Serum calcium was decreased and the bilirubin level increased with direct and indirect fractions about equal. Blood urea nitrogen (BUN) was elevated, serum albumin was depressed while the globulin content was elevated. Both direct and indirect Coomb's tests were negative. Treatment during the first three days consisted of 30 g mannitol, 1500 ml of whole blood and 1600 ml of packed cells given in an infusion. The whole blood was given when the hematocrit rose to 13%. During the second 24 hours after the injuries the patient received 7200 ml of intravenous fluids and excreted 2005 ml of urine. By the fifth day the patient was on the way to recovery.

Hematuria, hemoglobinuria and oliguria with hemoglobin casts characterized another observation made in a 46-year old man who sustained white phosphorus burns over 12.5% of his body. In spite of emergency debridement, cleansing of the wounds and vigorous intravenous fluid administration the blood and renal observations persisted. Hemodialysis was instituted and, hyperphosphatemia was noted during the month of hemodialysis; the patient eventually recovered (22).

Scherling and Blondis (23) have reported on damage and injuries to the eye resulting from chemical warfare agents. A male civilian munition worker (no age given) encountered a spill while working on the white phosphorus line. Twenty minutes after the accident an examination revealed smoking spots on the skin of his face and neck. Identical smoke was emanating from his conjunctival sacs. Eye examination showed particles of white phosphorus embedded in the bulbar and tarsal conjunctivae. Boric acid solution was applied immediately to irrigate the sacs and several drops of 2% Butyn were instilled, followed by drops of 3% copper sulphate solution. The boric acid irrigation stopped the smoking of the conjunctiva. The embedded particles were removed. Shortly thereafter the patient developed a slight blepharospasm which disappeared within the half-hour. 20/20 vision returned 12 hours later.

Although osseous effects have usually been associated with chronic phosphorus toxicity, Schautz (24) reported a case of bone necrosis of the feet following an acute phosphorus burn. While attempting to extinguish a fire after an air-raid in Germany a 38-year old woman sustained phosphorus burns to both feet and legs. She was hospitalized for apparent paralysis of the left arm and both legs following the burn. These symptoms were later attributed to polyneuritis caused by carbon monoxide poisoning. She recovered from the neurological disorder but due to the rather slow wound healing from the

phosphorus burns she had hospital treatment several times in the following 2 years. X-ray examination of the feet revealed a phosphorus-induced bone necrosis particularly in the metatarsals and phalanges with some observable periosteal reaction in the legs. Some particles of bone exited through purulent fistulae which had developed on the feet and three weeks later, as a result of excochleation, further fragments of bone exited from fistulae in the ball of the foot. The formation of fistulae subsided after Syncardon (pulse-wave massage) had been started. Recovery was gradual.

3. INHALATION TOXICITY OF WHITE PHOSPHORUS VAPOR

Aizenshtadt et al. (25) studied the acute inhalation toxicity of white phosphorus vapor in industrial workers. Five men whose ages were not indicated were exposed to white phosphorus vapors (0.035 mg/l of phosphorus and 0.22 mg/l of phosphorus pentoxide) while cleaning a tank of "Cottrell Milk" (aqueous suspension of phosphorite, quartzite and coke dust) by hand. They worked at the site for 2 to 6 hours at 7 hour intervals. While cleaning the tank from inside, the 5 men failed to wear their gas masks; this was the main cause of accidental inhalation. Six to 20 hours after completion of the work all 5 workers developed malaise, weakness, dry cough and slight hyperthermia (37.3-37.8°C). Their condition was exacerbated the next day. They had dyspnea, cough with thick discharge and high fever (39-39.8°C). Two of the 5 complained of headache, vertigo and chest pains with one having rhinitis and epistaxis.

Upon further examination it was found that 2 of the men had hyperemia of the face and pharynx. Multiple diffuse rales were found in all 5 men with 3 of them having bubbling rales. The liver was tender upon palpation in 4 of them but hepatomegaly (by 2 cm) was observed in only one patient. These aforementioned symptoms led to the diagnosis of tracheobronchitis in all 5 men. This was followed by roentgenologically verified toxic pneumonia in 3 of them. One patient had, in addition, toxic hepatitis.

There was indication of regional cerebral arterial hypotension in 4 patients (brachial arterial pressure; 120/60-140/90 mm Hg in all patients; maximal pressure in the temporal arteries = 15-30 mm Hg in 4 of them).

Blood tests were unremarkable except for a leukocytosis (9,350-14,500) with increased neutrophil count (69-87%) and relative lymphocytopenia (21-6%); the ESR (erythrocyte sedimentation rate) was increased to 20-51 mm/hour. Bilirubin did not exceed 0.35-0.53 mg% (indirect van den Bergh). Residual nitrogen level was normal (26-31 mg%). The cholesterol level was reduced (100-140 mg%). Dysproteinemia, typical of acute processes, was seen in all the 5 patients (albumin = 48.3 ± 2.3%; alpha-globulin fraction = 24.3 ± 3.2%).

Erythrocyte acetylcholinesterase (as determined by Hestrin's method) was reduced by 17% while that of plasma acetylcholinesterase was reduced by 35%. Mineral turnover was normal.

B. CHRONIC EFFECTS

Chronic white phosphorus toxicity has been seen mostly in factory workers who are exposed to phosphorus vapors for a considerable length of time. Ingestion, although rare, may be possible when foodstuff or fingers are soiled by particles or even fumes of white phosphorus (12). Generally, cases develop only after continual exposure for many years, although as little as 7 weeks occupational exposure has been described as resulting in intoxication. Cases have been reported among persons who had ceased working in the phosphorus-contaminated atmosphere many years before their symptoms appeared (11). In the reports of occupational exposure, factory sanitary conditions and the extent of exposure were not indicated. Early symptoms of chronic intoxication include gastrointestinal upset and sometimes a phosphorus odor (garlic-like) of breath. Cachexia and slight jaundice are common. The major effect is on the osseous system, especially the jaw (26). These effects are explained as follows:

EFFECTS ON THE OSSEOUS SYSTEM

Involvement of the osseous system is characteristic of chronic phosphorus intoxication. Most typical of this involvement is the "phossy jaw" or necrosis of the jaw. The first change in the bones is a generalized hyperostosis. The process is initially, a deposition of calcium salts, followed by resorption of these salts leading eventually to bone atrophy. As a result of these changes, fractures of the weight bearing bones frequently occur. There is ossification of the growing centers of the bones and the appearance in these bones of widened epiphyseal and sub-epiphyseal areas (11). The effect of chronic phosphorus exposure on the jaw bones producing necrosis is exemplified by the following case histories.

Miles (27) documented the case of a 35-year old lucifer-match maker who presented with external swelling and great debilitation. Prior to this presentation he had complained of pain in the jaw. There were several ulcerated openings along the line of the jaw from ear to ear; from these openings oozed a profuse discharge. In his mouth the toothless alveolar process was bared of soft parts in its entire extent. The jaw bone which was completely necrotic was surgically removed. It was found to be completely devoid of soft parts and periosteum, and brittle. This report gives no indication of the length of time the man worked in the match-factory.

A similar case of necrotic jaw bone was reported by Heimann (11) in a 35-year old man who had been employed in packaging yellow phosphorus for 13 years. A month prior to his illness dental x-rays were reported to be unremarkable. The disease began in the right maxillary first molar area and shortly thereafter in the corresponding area of the left maxilla. Despite extremely conservative surgical treatment the process extended to involve the upper palate and he lost a large portion of that bone. The condition led to fistulous tracts leading from the mouth into the nose and nasal accessory sinuses. It is noted that involvement of the upper jaw (maxilla) responds poorly to any type of therapy as compared to mandibular involvement. The extent of exposure to phosphorus vapor was not indicated; neither were the conditions of work reported.

Legge (28) documents several cases of chronic phosphorus toxicity-induced jaw bone necroses involving the upper and lower jaw. A 44-year old man worked as a process man on phosphorus condensers in a factory for 10 years. He presented with severe necrotic involvement of the left upper and right lower jaw. He was subjected to surgery and later re-assigned to light work. Right upper jaw necrosis was also observed in a 45-year old man who worked in the same work area for 23 years.

Simpson (29) explains that damage to the soft tissues around bone in chronic phosphorus toxicity enables suppurative bacteria to gain access to the bone and cause necrosis.

Chronic phosphorus toxicity-induced osseous necrosis associated with an abnormal peripheral blood picture was reported in a 36-year old man who worked in a phosphorus plant (30). The patient had previously had a lower left molar extracted from the site which later became a sequestrum. He worked in the phosphorus plant for 4 years before the diagnosis of jaw necrosis was made. Hematological studies were normal except for a reversed (abnormal) polymorphonuclear:lymphocyte ratio (30%:61%). No explanation was offered for this finding. There was delayed healing following bone biopsy from the iliac crest under prophylactic tetracycline and local anesthesia. The wound had been closed with penicillin powder and linen thread. Twenty days later the skin had not healed and an area of 1 cm^2 remained unepithelialized with some granulation tissue in the base and little discharge. The lesion healed normally later.

Kennon (31) described several cases of small carious sequestra in cyst-like cavities among workers in phosphorus plants. In one typical case, a 29-year old man was employed as a laborer at the plant for eighteen months. His dental condition at the time of employment was very poor. He had had 7 extractions and several fillings and scalings without any treatment. Seven months later after he had left the plant to join the Army he complained of sudden pain in the left side of his face. Upon admission to the hospital a wisdom tooth was extracted and subsequently submandibular drainage was established. Later radiologic examination confirmed osteomyelitis of the lower jaw and its proximity to the wisdom tooth indicated that there may have been some pre-disposing sepsis at the site.

Intense salivation as a symptom of chronic phosphorus intoxication was observed in a 23-year old man who worked for 5 months soldering tins containing phosphorus (28). Due probably to the brevity of his association with phosphorus, no necrosis of bone developed in this patient.

Von Oettingen (20) has stated in a review that salivation, ulcerative stomatitis and rapid deterioration of the teeth in a phosphorus factory worker should arouse the suspicion of chronic phosphorus intoxication. Additional symptoms which are pathognomonic of periostitis and incipient necrosis of the jaw bone are dull red spots on the mucous membranes of the oral cavity.

EFFECTS ON THE BLOOD

In chronic phosphorus intoxication, the level of potassium in the blood is low and those of chlorides and fat content are elevated. Leukopenia, anemia, and absence of methemoglobin gave also been reported (11).

URINARY CHANGES

Urinary changes in chronic phorphorus intoxications are reported to be elevated ammonia nitrogen at the expense of urea nitrogen, increased oxidized sulfur content, and albuminuria (11).

EFFECTS ON LIVER

No effects on the liver have been reported in chronic phosphorus intoxication (11).

EFFECTS ON CENTRAL NERVOUS SYSTEM

Although there is involvement of the central nervous system in acute intoxication, there is no evidence that chronic phosphorus exposure in man produces effects on this system (11).

GENERAL CACHEXIA

General cachexia has been reported in cases of chronic phosphorus intoxication. The symptoms described are loss of appetite, gastrointestinal upset, garlic-like breath, slight jaundice, and bleeding of the mucous membranes (11).

C. EPIDEMIOLOGY

Occupational white phosphorus intoxication was not coincident with the discovery of the element, but developed 150 years later when it began to be employed in the match industry in 1833. Cases of phosphorus intoxication have also been reported among workers manufacturing phosphorus, and in industries and trades using it. In Great Britain and Ireland there were 25 match factories during 1893-1898 employing 4,311 workers, 1,700 of whom worked in a process involving the use of white phosphorus. During those 5 years there were 37 reported cases of phosphorus necrosis. During 1915-1919 phosphorus necrosis underwent recrudescence in Great Britain when 21 cases were reported with 4 deaths. Twelve of these cases with one death occurred in a factory manufacturing white phosphorus (12, 32).

In Belgium 13 factories making matches during 1860-1895 employed about 2,600 workers. There were 34 cases of phosphorus necrosis (32). Likewise, seven factories in Denmark employed 76 adults and 180 children in 1874; within 5 years 11 cases of phosphorus necrosis occurred (32).

In Germany, in 1913, of 2 cases among 70 workers in a factory for making lights for miners' lamps, one recovered while the other was permanently disabled (12).

In Austria and Hungary, from 1881-1897, there were 140 cases of phosphorus necrosis in 90 factories manufacturing phosphorus matches; 47 of these cases occurred in one year (32).

In Norway 28 cases of phosphorus necrosis were reported between 1880 and 1893 among 600 workers involved in the match industry (32).

In Sweden there were 69 cases of necrosis between 1860 and 1870. From 1901 to 1905 there were 5,923 match workers (of whom about 1,100 were in phosphorus match factories); there were 27 cases of phosphorus necrosis. During 1906 and 1910 there were 6,558 match workers (of whom 1200 were making phosphorus matches); there were 15 cases of necrosis. From 1911 to 1915 about 7,172 workers were employed in match industries (of whom 600 were in phosphorus match factories); 6 cases of necrosis were reported (32).

During 1808-1809, fifteen match factories in the United States employed 3,591 persons, 2,024 men and 1,253 women 16 years of age and over, and 314 children under 16 years of age (121 boys and 193 girls). Of the workers 65 percent were employed under conditions exposing them to the fumes of phosphorus and to the dangers of phosphorus intoxication. A large percentage of the women and children were working in phosphorus processing, 95% of women and 83% of the children under 16 years. The cases of phosphorus necrosis reported were over 150; 4 of these were fatal. The length of employment of these workers was not mentioned (32). In 1925 a survey was conducted among workers employed in three fireworks plants in the United States. Phosphorus necrosis was reported in 14 out of 271 workers. Thirteen of the 14 cases were women. Among the employees who developed necrosis, one worker had been employed for more than 2 years. Another had been exposed to phosphorus for 6 months. Several others had been working in phosphorus for 2 years or less, 2 workers for 3 years, 2 for 5 years, and one for 6 years. Two of the 14 cases were fatal. In 9 out of 14 cases the necrosis developed in the lower jaw, in 4 in the upper jaw, and in one case in both jaws (32).

In France 5 cases of necrosis were reported in 1927 among workers in a white phosphorus factory; one case in a woman was caused by making phosphorated lighters for miners' lamps (12).

In the U.S.S.R., necrosis was found in 2 men who had worked 52 and 63 years respectively in a match factory. The illness had begun 40 years earlier and was exceedingly chronic. Several of these men's workmates had died in the meanwhile from phosphorus necrosis (12).

Some of the cases of phosphorus necrosis have been discussed in the preceding section on chronic effects.

XII. ANIMAL TOXICITY OF WHITE PHOSPHORUS

The toxicity of white phosphorus has been studied in various experimental animals. This section provides information on acute and chronic effects produced in animals after administration of white phosphorus by various routes. Acute effects are described after skin contact, subcutaneous injection, oral administration, and inhalation (of phosphorus vapors). Chronic effects are divided according to the organs or systems affected.

A. ACUTE EFFECTS

Skin contact with white phosphorus has produced burns at the site of application and extensive degeneration of hepatic cells. Generalized swelling in the kidneys with desquamation and perinuclear vacuolization and necrosis of cells of proximal tubules have also been observed. Subcutaneous injections have caused fatty infiltration of the liver, adrenal insufficiency and hemorrhagic kidneys. Oral intoxication has been responsible for liver damage and inhibition of osteocytic osteolysis and chondrolysis. Inhalation of phosphorus vapors has led to decreased hemoglobin and erythrocyte counts. The details of experiments and the findings are described as follows

1. SKIN CONTACT

White phosphorus was applied as a 0.1% solution in peanut oil (volume of application not given) to the skin of rabbits. There was no primary skin irritation in test animals at this concentration (33). A dermal sensitivity test in guinea pigs has not been reported.

It has been severally observed that when about 15% of the body surface is burnt by white phosphorus, death can ensue (34). To elucidate observations of sudden death following phosphorus burns in Vietnam, Bowen et al. (34) studied the phenomenon in 154 New Zealand white rabbits (no sex indicated) weighing approximately 3.5 kg (± 10%) for a period of 5 days. They set up a reproducible standard white phosphorus burn (SWPB) which was employed in the study. In a pilot study, post-burn serum analysis had revealed depression of calcium and elevation of phosphorus. These two parameters were hence the object of this study. After baseline blood studies had been done, the 130 rabbits (comprising Group 1) received SWPB which consisted of introduction of 10 g white phosphorus into a 7.5 cm area of the back. The white phosphorus was extinguished after 1 minute and the residue was removed immediately. The effective burn area was 10 to 20% of the total body surface area. Ninety of the 130 rabbits (of Group I) received no post burn treatment whereas in the other 40, the burn was totally excised and closed after 1 hour post burn.

Serum calcium and phosphorus levels were estimated pre-burn and at 12 hours, 1 day, 3 days and 5 days post-burn. Eighty-four of the 130 rabbits died, 75 dying within three days post-burn. There was no difference in the death rate between the untreated and the burn-excision subgroup. Blood samples revealed decreased serum calcium in 80% of the rabbits with more severe depression in the 84 that died. All animals that died had a significant ($p < 0.001$) elevation of phosphorus. The 45 control rabbits depicted normal serum parameters and there were no deaths in this group.

The 24 animals (comprising Group II) received the SWPB with no subsequent post-burn treatment. Calcium and phosphorus determinations were made hourly for the initial 12 hours post-burn. Blood samples were obtained from the inferior vena cava via a femoral vein catheter under Nembutal. Seventeen of the 24 rabbits died, with 18 of them dying within 24 hours post-burn. One-hour after burn, depression of serum calcium and elevation of serum phosphorus were noted in those animals which died. The 7 which survived showed only minor calcium-phosphorus shifts. No deaths occurred in the ten rabbits comprising the Group II controls and their serum calcium and phosphorus levels were within the normal range. There was no cogent explanation for the increased mortality and more rapid calcium and phosphorus changes in Group II as compared to Group I except mention of the possibility that the sedation (Nembutal) used in Group II may have potentiated the action of white phosphorus.

Ben-Hur et al. (35, 36) studied the causes and mechanisms involved in death following acute phosphorus burn in rats. The pathophysiology of phosphorus burn was studied in 5 groups of 10 Hadassah-bred male rats per group. Each rat weighed approximately 350 g. In Group I after intraperitoneal injection of sodium pentothal, 50 mg of white phosphorus were introduced into a 1.5 cm longitudinal incision made in the inguinal region. The phosphorus was ignited but restrained from rapid burning and undue spreading by opening and closing the wound until active combustion stopped. Group II rats received a similar treatment, however, with only 10 mg of white phosphorus. In Group III, 50 mg of white phosphorus were introduced into the incision but it was not ignited. The wound was closed immediately. Groups IV and V were the controls. Group IV rats were merely anesthetized while Group V rats were anesthetized and burned with a brass plate heated to 100°C producing a third degree burn which covered 15% of the body surface. All rats were housed in metabolic cages with abundant food and water.

Fifty percent (fifteen) of the white phosphorus-burned rats died within 3 to 4 days. In the clinicopathological assessment, the "phosphorus-burn" group was put together with no distinction being made as to the amount of white phosphorus involved in the burn. Smoke emanated when the wounds were opened and the burned surfaces appeared necrotic, smelling of garlic for about 2 days. No healing occurred for 6 days post-burn. Those animals which survived were sacrificed for additional histopathological assessment. No mention was made about deaths or clinicopathologic assessment of the rats which received metal burns and consequently no comparison could be made between pathologic changes due to phosphorus burn and those due to metal burns. The biochemical evaluation of the phosphorus burned rats is depicted in Table 7. Serum phosphate concentrations began rising 2 hours post burn, reaching 11 mg% at 24 hours post-burn (normal 4-5 mg%) without a concomitant decrease in serum calcium. During the 36 hours after the phosphorus burn 10 of the rats had plasma urea nitrogen (PUN) values over 100 mg% (normal 10-12 mg%) with low sodium values of 125-130 milliequivalents per liter (normal 135-143 milliequivalents per liter) and rather high levels of potassium values in excess of 8 milliequivalents per liter (normal 4-5 milliequivalents per liter). Serum glutamic-pyruvic transaminase (SGPT) was greater than 100 units/ml (normal 10 units/ml) in 15 rats. Creatinine clearance began to drop from 72 hours onwards, but began to rise in surviving

rats on the 4th and 5th days post-burn. Histopathologically there was extensive degeneration of hepatic cells with microthrombi in the portal veins. In the kidneys there was generalized swelling with desquamation and perinuclear vacuolization and necrosis of cells of the proximal tubules (35). These results were also confirmed by other studies (36, 37).

TABLE 7
BLOOD AND URINE BIOCHEMISTRY IN THE PHOSPHORUS BURNED RATS

Item	Normal	Phosphorus Burns after 72 hours
Water intake (ml/day)	16(15-18)	45 (40-50)
Urinary output (ml/day)	11 (10-12)	35 (30-40)
Serum PO_4 (mg%)	4.5 (4-5)	10 (10-11)
Serum Urea (mg%)	15 (10-20)	100
Serum Na (mEq/1)	140 (135-143)	127 (125-130)
Serum K (mEq/1)	4.5 (4-5)	8
SGPT (U/ml)	10	100
Serum osmolality (mole/1)	292	350
Urine osmolality (mole/1)	2,100	700
Creatinine clearance (ml/min)	1.25	0.75

Ref: Ben-Hur et al. (35).

2. SUBCUTANEOUS ADMINISTRATION

Bodansky (38) studied metabolic pathologic effects of phosphorus toxicity with regard to blood glucose levels in a female dog weighing 13.0 kg which was given a single subcutaneous injection of 0.38 mg/kg white phosphorus in olive oil. On the first day pre-injection, the assessed blood sugar was 0.096%. Three days after injection the blood sugar level was 0.108%. Another 0.38 mg/kg body weight of white phosphorus in olive oil was injected subcutaneously into the dog. Three days thereafter the blood sugar level was 0.068%. Although no statistical evaluation was offered it appears that the difference between the pre-intoxication and the post-intoxication blood sugar levels is not significant.

Blood, urine and tissue pathologies caused by white phosphorus intoxication were studied by Buchanan et al. (39) in 16 one-year old female dogs (no breed indicated) weighing 10 kg. Three dogs received single doses of 0.4 mg/kg body weight white phosphorus in peanut oil subcutaneously. Three days post-injection, these dogs had hematemesis and died by the sixth day. All organs showed marked vascular engorgement. Apart from a limited area (zone around the central veins) which had fatty metamorphosis, necrosis encompassed the entire parenchymal tissue of the liver. Extensive necrosis was also observed in the renal tubules and fatty degeneration was seen in the less severely damaged renal areas.

One dog received a single dose of 0.2 mg/kg body weight. Blood was seen in the cage on the 9th day when the dog died. The liver was hemorrhagic at autopsy

and consolidated with fatty vacuolation particularly around the periphery of the lobules. There were also areas of hemorrhaging in the kidney.

The remaining 12 dogs received single doses of 0.1 mg/kg body weight subcutaneously. On day 53, one dog lost appetite and died suddenly on the 55th day. On day 116 all dogs which had survived were sacrificed. No significant fatty infiltrations in the liver and kidneys were observed in this group that received 0.1 mg/kg body weight. These dogs had hydropic degeneration of the kidney and hemorrhaging in areas of the livers. There were also histological signs of nephritis.

Urine studies revealed high creatine to creatinine ratios in all three dogs receiving 0.4 mg/kg, the dog given 0.2 mg/kg and one of the 12 dogs administered 0.1 mg/kg. No hematological findings of pathological consequence were noted in the dogs which received 0.2 mg/kg or 0.1 mg/kg body weight of white phosphorus.

A study of white phosphorus toxicity centered on the liver was made by Lueding and Ladewig (40) in guinea pigs (number not specified). The animals were given subcutaneously 7.5 mg/kg body weight of white phosphorus in olive oil and the livers were excised three days after the initial injection. Production of glucuronic acid by these surviving liver slices was noted to be inhibited by the phosphorus injection. Histologically the livers were infiltrated with fatty deposits and consolidated with parenchymal necrosis and nuclear swelling.

By means of subcutaneous injections to mice, Scott (41) studied the toxicity of white phosphorus in mitochondria. Phosphorus solutions in the concentrations of 0.0125% to 0.05% in volumes of 0.1 to 0.2 ml were injected into white mice (number of mice, strain and sex not indicated). There was no uniformity in the protocol of white phosphorus administration to the mice. Doses were given at intervals of a day or more (for a longer or shorter time) depending upon whether a severe or a slight reaction was the objective. There was no indication as regards the dose per day per mouse. When it was determined that sufficient toxic effects could be noticed, the mice were sacrificed, the pancreas was removed, stained and examined microscopically. The findings were those of gradual to gross morphological deformations of the mitochondria. No indication was given as to what dose was responsible for what level of morphological deformation.

Subcutaneous injections of 1.6 to 10 mg/kg body weight of white phosphorus in oil induced adrenal insufficiency in rabbits (42). Sixteen rabbits (two of which were controls) were studied (see Table 8). Four rabbits which were given 2.5 mg/kg, 4.7 mg/kg (3 injections within 96 hours), 6.05 mg/kg and 6.5 mg/kg, respectively, had fatty infiltrations of the liver and appeared to have no epinephrine as indicated by the negative iodine-ferric chloride test. Eight rabbits had no fatty livers but were devoid of chromaffin reaction. These rabbits received two injections of 8.30 mg/kg, 1.6 mg/kg, 1.9 mg/kg, 2.4 mg/kg, 5.0 mg/kg, 3.7 mg/kg, 3.9 mg/kg, and one injection of 4.1 mg/kg, respectively. Two animals given doses of 1.9 mg/kg or 10 mg/kg had fatty livers but no chromaffin substance.

The effects of acute phosphorus toxicity on the chylomicron count were determined in 27 adult rats which were given large doses of white phosphorus subcutaneously (43).

TABLE 8.
ADRENAL INSUFFICIENCY CAUSED
BY ACUTE PHOSPHORUS TOXICITY IN RABBITS

Number of Rabbit	Dose mg/kg	Time killed or died	Histological and Histochemical Findings	Weight of Rabbit (kg)
1	Control	3 days	Abundant chromaffin substance	3.1
2	Control	2 days	Abundant chromaffin substance	2.9
3	*6.05x2	60 hours	Fatty liver; I-$FeCl_3$ test negative	3.3
4	*8.30x2	died 60 hours	I-$FeCl_3$ negative	1.2
5	+6.5x3	96 hours	Fatty liver; I_2Cl_3 test negative	3.1
6	+4.7x3	96 hours	Fatty liver; I_2 reaction negative	3.5
7	2.5	78 hours	Fatty liver; no chromaffin substance	3.0
8	*1.6x2	124 hours	Reduced chromaffin substance	1.5
9	*1.9x2	75 hours	No chromaffin substance	2.7
10	*1.9x2	75 hours	Fatty liver; no chromaffin substance	2.7
11	10	died 32 hours	Fatty liver; no chromaffin substance	3.4
12	*2.4x2	died 56 hours	No chromaffin in 1 adrenal; trace in other	3.65
13	*5x2	died 60 hours	Fatty liver; no chromaffin	3.0
14	*3.7x2	died 68 hours	No fatty liver; no chromaffin reaction	2.8
15	*3.9x2	83 hours	No fatty liver; no chromaffin reaction	2.7
16	4.1	died 122 hours	No fatty liver; no chromaffin reaction	1.40

Ref: Neubauer (42).
* dose was given twice
+ dose was given thrice

Group 1 (consisting of 15 rats, sex not indicated) rats received 1.1 mg/kg body weight/day of white phosphorus in peanut oil three times per week for 45 days. Group 2 (12 rats) served as controls. Throughout the experiment, the rats receiving phosphorus showed elevated base count, see Table 9. However the extent of elevation was so slight as to make it of doubtful significance.

An increase in the number of circulating monocytes was found in guinea pigs following subcutaneous injections with white phosphorus (44). Thirteen guinea pigs received on the average 1 mg/kg body weight subcutaneously at intervals of 3 to 5 days, receiving a total of 7 to 11 mg white phosphorus, after which the animals were sacrificed. Total and differential counts of white cells were made daily for several days before and during the period of injections. The monocyte count increased from a mean of 971 before injections to 1638 after the sixth and last injection. Variations in the other white cells were unremarkable with the exception of one guinea pig which showed a marked leukocytosis (31,200) with a monocyte count of 5615 (44).

3. ORAL ADMINISTRATION

The oral LD_{50} in male and female rats has been reported as 3.76 and 3.03 mg/kg body weight, respectively. In mice the oral LD_{50} has been reported as 4.85 and 4.82 mg/kg body weight for males and females, respectively. Death occurred over a period of several days. Animals of both species became anorexic and exhibited yellow and enlarged livers (33). The oral LD_{50} in other animals has not been reported.

Williamson et al (45) studied the acute toxicity of white phosphorus in 8 dogs. The dogs (strain, sex and age not indicated) were given capsules of cod-liver oil containing 0.05 mg phosphorus until they died. Each dog was given 2 capsules per day (0.10 mg/day = 0.01 mg/kg body weight/day) although the length of the study period was not indicated. Hence one could not estimate how much phosphorus was responsible for the noted effects. There was marked terminal hypoglycemia in three of the dogs; the livers were unremarkable, but six of them had hyperuricacidemia.

The pathogenesis of abnormal remodeling of bones caused by acute white phosphorus toxicity was studied by Whalen et al (46) in 16 female Wistar rats which were 23 days old. Four rats were fed a test diet containing 1.30 mg/kg body weight/day of white phosphorus for 16 days and then sacrificed with 4 controls which had been kept on stock diet. Another 4 rats were fed the test diet (1.30 mg/kg/day) phosphorus for 8 days and were killed with four controls kept on stock diet.

After 16 days of 1.30 mg/kg/day of white phosphorus ingestion metaphyseal trabeculae of proximal tibiae were observed to be wider and the metaphysis was broadened. Normal metaphyseal density and tapering occurred after withdrawal of the poison. In both the rats kept on the test diet for 16 days and in those for 8 days there was definite inhibition of osteocytic osteolysis and chondrolysis. This inhibition led to widening of the trabeculae and retention of the chondroid core. No mention was made in the study about differences in effects between the 8-day treated rats and the 16- treated rats.

Acute phosphorus toxicity-induced fatty infiltration and/or degeneration of the liver was studied by Pani et al (47) in 64 female Sprague-Dawley rats

TABLE 9

GROUP MEAN BASE CHYLOMICRON COUNTS

Group	Before Injection Began	Base Chylomicron Counts Chylomicrons per Field — Day of Experiment													
		3	5	7	10	12	14	17	21	24	26	28	31	39	45
1. Phosphorus intoxicated animals (15 rats)	18.6	20.0	19.6	19.4	19.8	19.3	19.3	19.0	19.0	19.5	19.0	19.0	18.7	18.3	19.0
2. Control animals (12 rats)	18.6	17.3	18.3	18.3	18.0	18.8	18.8	17.3	18.5	18.5	17.7	18.0	18.8	18.7	18.7

Ref: Fleming et al. (43)

weighing 200 to 300 g. The rats were divided into 5 groups, the first group consisting of 5 rats serving as control. Experimental treatment of the rats consisted of a single dose of 10 mg/kg body weight of white phosphorus by stomach tube. The control group received the equivalent amount of mineral oil.

The second group consisting of 9 rats, was pretreated by intraperitoneal injection of phenobarbital (PB) (a microsomal enzyme inducer) as a 0.8% solution in 0.9% saline in the amount of 80 mg/kg body weight at 72 and 48 hours, 50 mg/kg body weight at 24 hours, and 30 mg/kg body weight at 12 hours prior to administration of white phosphorus (10 mg/kg body weight) to 4 of them.

The third group consisting of 9 rats received intraperitoneally N, N'-diphenyl-p-phenylenediamine (DPPD) suspended by homogenization in 2.5% acacia gum in water containing Tween 80 (0.25% v/v) in the amount of 500 mg/kg body weight 48 and 24 hours prior to administration of white phosphorus (10 mg/kg) to 4 of them.

The fourth group of 11 rats received propyl gallate (PG) as a 3% solution in 0.9% sodium chloride in the amount of 300 mg/kg body weight intraperitoneally 1 hour before the administration of white phosphorus (10 mg/kg) and again 6 hours after phosphorus injection in the amount of 100 mg/kg body weight to 5 of them.

The fifth group of 15 rats received glutathion (GSH) as an 8% solution in 0.9% sodium chloride in the amount of 800 mg/kg body weight intraperitoneally 30 minutes before the administration of white phosphorus (10 mg/kg body weight) to 7 of them. The rats had free access to water after the intoxication and they were all killed 12 hours after injection except those animals involved in the assessment of the effect of DPPD, GSH, and PG on polyribosome disaggregation induced by white phosphorus.

Hepatic diene conjugation of microsomal lipids was assayed; also the total lipid extraction was done. A study was also made of polyribosomal patterns.

Triglycerides were observed to accumulate in poisoned rats within 4 hours. The maximum degree of fat infiltration occurred at 12 hours.

Phenobarbital did not alter the level of hepatic triglycerides induced by phosphorus toxicity nor did DPPD exert any protective effect on troglyceride accummulation in the livers of the intoxicated rats (see Table 10).

Glutathion and propyl gallate exerted a protective effect upon triglyceride infiltration of the liver of rats treated with phosphorus as shown in Table 11.

TABLE 10
EFFECT OF DPPD AND PB PRETREATMENT ON
HEPATIC TRIGLYCERIDES IN WHITE PHOSPHORUS
INTOXICATION

TREATMENT	LIVER TRIGLYCERIDES (mg/100 g body weight)	Number/group
	Mean ± S.E.M.	
(a) Control	36.34 ± 8.97	(5)
(b) Phosphorus	180.71 ± 16.54	(5)
(c) DPPD	29.98 ± 6.59	(5)
(d) DPPD + phosphorus	180.55 ± 11.73	(4)
(e) PB	84.88 ± 14.46	(5)
(f) PB + phosphorus	180.73 ± 11.14	(4)

Ref: Pani et al, (47).

Statistical significance of the differences, P value by the t test:

a-b, c-d, e-f: < 0.001;
a-c, b-d, b-f: not significant; a-e: < 0.100

TABLE 11
EFFECT OF GSH AND PG ON THE LEVELS OF HEPATIC TRIGLYCERIDES IN WHITE PHOSPHORUS INTOXICATION

	TREATMENT	LIVER TRIGLYCERIDES (mg/100 g body weight)	Number/group
		Mean ± S.E.M.	
	A		
a)	Control	18.080 ± 1.80	(8)
b)	Phosphorus	95.00 ± 11.93	(7)
c)	GSH	12.92 ± 1.32	(8)
d)	GSH + phosphorus	31.53 ± 9.94	(7)
	B		
e)	Control	26.95 ± 5.21	(5)
f)	Phosphorus	108.14 ± 15.03	(5)
g)	PG	30.85 ± 4.07	(6)
h)	PG + phosphorus	29.95 ± 6.54	(5)

Ref: Pani et al. (47).

Statistical significance of the differences, P values by the t test:
a-b, b-d, e-f, f-h: < 0.001; a-c: < 0.050
e-g: not significant.

In the assessment of diene conjugation of microsomal lipids in rats intoxicated with phosphorus and pretreated with DPPD and PB it was found that lipid peroxidation is not a necessary step for development of fatty liver caused by white phosphorus.

Disaggregation of polyribosomes with reduction in the amount of heavy aggregates and concurrent increase in monomeric-dimeric ribosomes was induced by phosphorus toxicity. DPPD pretreatment did not affect the degree of disaggregation induced by phosphorus whereas the assembly indices of polysomes in phosphorus treated rats, but given GHS or PG, were similar to those of the controls (see Table 12).

TABLE 12
EFFECT OF DPPD, GSH AND PG ON
POLYRIBOSOME DISAGGREGATION INDUCED
BY WHITE PHOSPHORUS

TREATMENT	ASSEMBLY INDEX	Number/group
	Mean ± S.D.	
Control	1.46 ± 0.08	(3)
Phosphorus	0.72 ± 0.07	(5)
DPPD + phosphorus	0.61 ± 0.06	(3)
GSH + phosphorus	1.32 ± 0.13	(3)
PG + phosphorus	1.21 ± 0.09	(3)

Ref: Pani et al (47).

No analysis as to the statistical significance of this study was undertaken.

A summary of pathologic observations made in the acute toxicity of white phosphorus in animals is depicted in Table 13.

4. EYE IRRITATION

White phosphorus applied as a 0.1% solution in peanut oil (volume of application not specified) to the eyes of rabbits did not produce any irritation (33).

5. INHALATION

Inhalation of phosphorus vapors by rabbits at vapor concentration of 150-160 mg/m^3 half an hour daily for sixty days produced a decrease in hemoglobin and erythrocyte counts (48). The lowest lethal concentration for mice has been reported as 500 mg/m^3 (10 minutes) (49).

TABLE 13

PATHOLOGIC OBSERVATIONS MADE
IN ACUTE TOXICITY STUDIES OF WHITE PHOSPHORUS IN ANIMALS

SPECIES	DOSE	ROUTE OF ADMINISTRATION	TOXICITY OBSERVATION	REFERENCE
Mice	0.0125%	subcutaneous	Morphological deformation of the mitochondria	Scott (41)
	0.05%	subcutaneous		
	4.82-4.85 mg/kg	oral	LD_{50}, anorexia, jaundiced and enlarged liver	Lee et al. (33)
	500 mg/m^3	inhalation	Death within 10 minutes	NIOSH (49)
Rabbits	0.1% in peanut oil	skin application	No skin irritation	Lee et al. (33)
	1.6-10 mg/kg	subcutaneous	Adrenal insufficiency	Neubauer (42)
	3,000 mg/kg	skin application	Burns, decrease in serum calcium, increase in serum phosphorus	Bowen et al. (34)
	150-160 mg/m^3	inhalation	Decrease in hemoglobin and erythrocyte counts	Maruo (48)
Rats	140 mg/kg	skin application	Burns, changes in blood and urine biochemistry, fatty degeneration and nephritis in kidneys	Ben-Hur et al. (35)
	3.03-3.07 mg/kg	oral	LD_{50}, anorexia, jaundiced and enlarged liver	Lee et al. (33)
	10 mg/kg	oral	Fatty infiltration and/or degeneration of liver, biochemical changes in liver	Pani et al. (47)
Dogs	0.05 mg/kg	oral	Fatty degeneration of liver and hepatic insufficiency	Williamson (45)
	0.2-0.4 mg/kg	subcutaneous	Gastrointestinal lesions	Buchanan (39)
	5 mg/kg	subcutaneous	Fatty degeneration of liver and hepatic insufficiency	Bodansky (38)

B - CHRONIC EFFECTS

Chronic toxicity in experimental animals after oral administration of white phosphorus has been shown to produce reduced weight gain, retardation of longitudinal bone growth, liver cirrhosis, and shifts in plasma proteins. Subcutaneous doses in dogs have produced hydropic renal degeneration and intravenous administration to rabbits has shown nerve degeneration in the central nervous system. These effects are described as follows.

EFFECTS ON GROWTH

The effect of the chronic oral administration of 0.003 to 0.07 mg/kg/day of white phosphorus on the rate of weight gain in animals was studied in 32 rats (22 young females and 10 mature males) over a period of 5 to 6 months (50). Ten young female rats given 0.07 mg/kg/day for 22 weeks showed a decreased weight gain as compared to normal growth charts. When the poison was withdrawn there was no appreciable recovery. Similar findings were made in the group of 6 young female rats given 0.018 mg/kg body weight/day for 22 weeks, except that upon withdrawal of the poison, recovery in growth (as judged by rate of weight gain) occurred. The group of 6 young female rats given 0.0032 mg/kg body weight/day for 22 weeks did not show any ill-effects until the 15th week, when a slight reduction in weight gain was observed. Ten adult male rats given 0.0027 mg/kg body weight/day for 25 weeks showed very little reduction in weight gain and attained expected weight when poisoning was discontinued. However, the lack of controls and statistical analysis leaves the significance of these findings in doubt.

Fourteen rats were given 0.01% white phosphorus in cod liver oil in the diet for periods varying from 22 to 57 days. In the diet of 6 of these rats the white phosphorus was increased to 0.04% during the last week of the experiment. The animals receiving white phosphorus in their diet failed to gain as much weight as did the controls (51).

Rabbits given oral doses of 0.3 mg/kg body weight/day for 117 days showed an overall reduction in weight gain as compared to controls (51).

EFFECTS ON GROWING BONE AND GROWING TEETH

A decrease in the longitudinal growth of tibias occurred when rabbits and rats (34 rabbits and 28 rats) were subjected to chronic white phosphorus intoxication (51). The rabbits (17 probands) received 0.3 mg/kg body weight/ day orally for up to 117 days, while among the rats 8 received 0.01% white phosphorus in the diet (in cod liver oil) and 6 received 0.01% white phosphorus in cod liver oil for 1 to 50 days followed by 0.04% phosphorus from the 50th to 57th day. Seventeen rabbits and fourteen rats served as respective controls. The average daily growth of the tibial diaphysis was 0.27 mm in those rabbits receiving white phosphorus as compared to 0.36 mm per day in the controls. No roentgenographic changes were found in the teeth of animals receiving white phosphorus but in the skulls phosphorus bands were observed on both sides of the basispheno-occipital and basisphenopresphenoid junctions in the poisoned animals. The rats whose phosphorus dose was increased to 0.04% daily had a calcictraumatic line in the labial dentin. This was absent in rats receiving the 0.01% dose. In the intoxicated rabbits the epiphyseal plate was narrow and the diaphyseal marrow became less cellular as compared to the controls.

One hundred twenty male and female rats exposed to white phosphorus vapors at concentration of 150-160 mg/m^3 half an hour daily for 60 days had widened epiphyseal lines, irregularity of cell configuration, remarkable trabeculation associated with insufficient ossification and disordered axile development of long bones (52).

EFFECTS ON LIVER

Mitotic nuclear divisions in fat storing and Kupffer cells in the liver during chronic phosphorus intoxication were observed in rabbits by Tsunoda (53). One hundred and thirty four rabbits (no strain or sex indicated) were divided into two groups (number of animals per group was not indicated). Group A rabbits were given 1% while Group B rabbits received 3% phosphorus in oil orally (3-14 drops daily). The animals were observed for 50 days, thereafter their livers were examined histologically. Compared to controls (number of animals in the control group was not indicated) there was an increase in the mitoses of fat storage cells in the sinusoid walls of the lobes, and the Kupffer cells showed increased mitotic nuclear divisions. The parenchyma revealed gross histopathological changes, but the overall picture of fatty infiltration was very slight as compared to observations made in acute toxic cases. Group B rabbits had a greater reduction in glycogen content of hepatic cells than Group A rabbits, and the nuclear mitotic divisions were more pronounced and intense in Group A than in Group B rabbits. Both groups, however, revealed morphological deformation of the mitochondria to the same extent.

Contrary to some previous reports of insignificant hepatic effects in chronic phosphorus toxicity (39, 54), Mallory (55) demonstrated 0.6-1 mg/kg body weight/day of yellow phosphorus administered orally in a 0.2% solution of oil of sweet almonds, to rabbits and guinea pigs, definite liver cirrhotic changes. The induced hepatic changes were often complicated by ascites and jaundice. Eighty five rabbits and guinea pigs were used in the study but numbers per species were not indicated nor was there a breakdown of the respective dosages per species and effects noted at each dose level. The chronic phosphorus-induced toxic injuries were directed to stromal fibroblasts, particularly in the area of the portal vessels as well as parenchymal cells throughout the lobule. Dysfunction of cells was more massive, with active regeneration (as noted by the numerous mitotic figures) when the administered dose was 1 mg/kg/day, but these effects were decreased considerably when the dose was lowered to 0.33 mg/kg body weight. The shortest time required to produce the degenerative changes characteristic of hepatic cirrhosis was four months.

Fifty one guinea pigs weighing from 300 to 500 g were studied in two groups. One group received 0.75 mg/kg body weight orally four days a week and the other group received 1.5 mg/kg body weight orally twice per week. The experiment lasted 35 weeks and 2 to 4 animals were sacrificed at irregular intervals. After 9 weeks all livers studied showed loss of parenchymal substance. This event spread to more lobes as the period of testing lengthened. There followed atrophy of the lobes side by side with hypertrophy of uninvolved lobes and general signs of pre-cirrhosis. Failure to produce clear-cut portal cirrhosis seems to be due to inconsistent and minimal degree of periportal necrosis (56).

EFFECTS ON PLASMA PROTEINS

Plasma protein shifts induced by chronic white phosphorus intoxication were studied in 8 dogs (7 male and 1 female). The dogs were subjected to oral admin-

istration of 0.2 mg/kg to 0.8 mg/kg body weight daily for 37 days. The white phosphorus was administered in Oleum phosphoratum containing 0.01 g phosphorus. At selected periods during the chronic intoxication blood samples were taken for the evaluation of plasma protein: albumin, globulin and fibrinogen. By the end of the experimental period there was a decrease in plasma albumin (except for Dogs 5,7,8) and fibrinogen (except for Dogs 3,4,6) and an increase in globulin (except for Dog 6). No statistical analysis was offered to indicate the levels of significance (57). Table 14 summarizes the results of this experiment.

EFFECTS ON KIDNEYS AFTER SUBCUTANEOUS DOSES

Chronic phosphorus toxicity has been reported in 16 adult dogs (sex and pedigree not indicated) which were subjected to prolonged and repeated subcutaneous injections of 0.1 mg/kg body weight/day for 56 days. The pathological observation made was that of hydropic degeneration in the kidneys. No definite necrotic processes could be observed in the bones, nor was there any fatty infiltration of the liver. The tissue breakdown is presumed to have caused an increase in the loss of creatine (39).

EFFECTS ON CENTRAL NERVOUS SYSTEM

Ferraro et al (54) described pathological changes which occurred in brains of 15 adult rabbits which received a 1% solution of phosphorus in oil (0.2 to 1.0 ml doses) intravenously twice or thrice per week over a period of 15 weeks. The rabbits were killed and autopsied and by means of standard neuropathologic techniques ; various regions of the central nervous system were examined. Important degenerative processes found included granular disintegration of Nissl bodies, displacement, hyperchromatosis and shrinking of the nuclei of ganglion cells as well as vacuolation and liquefaction of the cytoplasm. Nerve cells of the inferior olives appeared to have more severe lesions than cells in other areas of the brain; there was no detectable fatty infiltration. There were occasional perivascular infiltrations of lymphoid and plasma cells in areas such as the meninges which portrayed signs of inflammatory reaction. There was hyperplasia of the glia coexisting with hypertrophic changes , often leading to formation of monster cells.

Prolonged administration of 0.04 mg/kg/day to white rats (route unspecified) resulted in an intensification of excitatory processes and increased cortical excitability (58).

The chronic effects in animals after white phosphorus intoxication are summarized in Table 15.

TABLE 14

EFFECT OF CHRONIC WHITE PHOSPHORUS INTOXICATION ON PLASMA PROTEINS

Dog #	EXPT. Day	PERCENT OF TOTAL PROTEIN Albumin		Globulin		Fibrinogen	
1	1	60.25		27.77		11.96	
	26	57.10	↓	33.41	↑	9.47	↓
2	1	60.38		28.26		11.34	
	34	52.71	↓	36.74	↑	10.54	↓
3	1	36.16		32.39		11.30	
	31	33.19	↓	34.59	↑	12.20	↑
4	1	64.96		29.92		5.11	
	24	58.19	↓	34.08	↑	7.71	↑
5	1	57.72		30.43		11.83	
	17	58.19	↑	38.46	↑	3.34	↓
6	1	57.30		30.33		17.24	
	37	54.20	↓	30.08	↓	15.71	↑
7	1	54.74		28.01		17.24	
	30	59.67	↑	36.72	↑	3.60	↓
8	1	55.81		28.37		15.81	
	14	58.38	↑	33.53	↑	8.08	↓

Ref: Lang (57)

↑ increased when compared to Day 1

↓ decreased when compared to Day 1

TABLE 15
CHRONIC WHITE PHOSPHORUS TOXICITY IN ANIMALS

Species	Dose and Route of Administration	Duration of Administration	Outcome	Reference
Dogs	0.1 mg/kg body weight/day (subcutaneous)	56 days	Hydropic renal degeneration	Buchanan (39)
	0.2-0.8 mg/kg body weight/day (oral)	37 days	Shifts in plasma proteins	Lang (57)
Rats	0.0027 mg/kg body weight/day (oral)	25 weeks	Slight reduction in weight gain	Sollman (50)
	0.0032 mg/kg body weight/day (oral)	22 weeks	No ill effects until 15 weeks after which slight reduction in weight gain.	Sollman (50)
	0.018-0.07 mg/kg body weight/day (oral)	22 weeks	Reduction in weight gain	Sollman (50)
	0.01% in cod liver oil (oral)	22-57 days	Reduction in weight gain and retardation of longitudinal bone growth	Adams (51)
Guinea pigs and rabbits	0.6-1 mg/kg body weight/day (oral)	4 months	Liver cirrhosis	Mallory (55)
Guinea pigs	0.75 mg/kg body weight four days/week (oral)	35 weeks	Destruction of hepatic parenchyma	Ashburn (56)
Rabbits	0.3 mg/kg body weight/day (oral)	117 days	Reduction in weight gain and retardation of longitudinal bone growth	Adams (51)
	0.2-1 ml of 1% solution of phosphorus in oil twice or thrice per week (intravenous)	15 weeks	Nerve degeneration in central nervous system	Ferraro (54)

XIII. INHALATION TOXICITY OF WHITE PHOSPHORUS SMOKE

The toxicity described in this section is for white phosphorus smoke, but the toxicity for red phosphorus smoke should be similar since the combustion products from either white phosphorus or red phosphorus are the same; however, no studies for red phosphorus smoke have been reported in the literature.

White and Armstrong (59) have established that white phosphorus smoke is composed principally of phosphorus pentoxide (P_2O_5) [with possible small amounts of phosphoric acid depending upon atmospheric humidity]. A Mitscherlich test run on the minced carcasses of mice which had been killed with white phosphorus smoke revealed no elemental phosphorus (59).

EFFECTS ON HUMANS

It has been estimated that the minimum harassing concentration of white phosphorus smoke for men doing work is about 700 mg/m^3 (6). This is the concentration which mandates wearing of masks. At concentrations beyond 1000 mg/m^3, the smoke is unbearable to most people. There are no available data on the concentrations of phosphorus vapor which are associated with occupational phosphorus intoxication (6).

Forty men were studied for white phosphorus smoke toxicity (59). The men (ages not indicated) were exposed to varying concentrations of white phosphorus smoke for 2 to 15 minutes. Of the 7 men who were exposed to 188 mg/m^3 for 0 to 5 minutes, two experienced neither coughing nor throat irritation during exposure and five experienced throat irritation, coughing and slight headache during that exposure period. Twenty four hours later only four of them had frontal headache, nasal congestion, throat irritation with some discharge and coughing. After two and three days only one showed any signs of respiratory irritation (59).

Of the 5 men who were exposed to 408 mg/m^3 for 0 to 10 minutes, all but one of them had throat irritation and cough during the exposure period. During the three days post-exposure only one subject experienced throat soreness with symptoms of a cold (59).

At a concentration of 425 mg/m^3 for 0 to 15 minutes, all six men experienced throat and nasal irritation during exposure but barely any remarkable effects during the three days post-exposure.

At a concentration of 453 mg/m^3 for 0 to 10 minutes all save one of six men experienced sharp throat irritation upon talking, and one of this group felt nauseated and discharged from the nose during the three days post-exposure.

All seven men subjected to 514 mg/m^3 for 0 to 16 minutes had nasal and throat irritation and coughing during the period of exposure; three subjects from this group had no effects during the six days post exposure.

The other two proband groups who were subjected to 588 mg/m^3 for 2 minutes and 592 mg/m^3 for 3.5 minutes exhibited the basic signs of respiratory distress, nasal discharge, coughing and throat irritation and soreness upon talking (59).

Collumbine (60) exposed a total of 108 men to white phosphorus smoke concentrations ranging from 87 to 1770 mg/m^3 (length of exposure not specified); the results were those of throat irritation and coughing. He established the minimum harassing concentration of white phosphorus smoke for men doing work at 700 mg/m^3 and for those at rest at 1000 mg/m^3. The effects of phosphorus smoke on humans upon inhalation are summarized in Table 16.

EFFECTS ON ANIMALS

In an extensive study of the toxicity of white phosphorus smoke in mammals other than humans, 240 mice (in 12 runs of 20 mice per run), 330 rats (in 33 runs of 10 rats per run) and 60 "brush" goats (in 14 runs of 3 goats and 3 runs of 6 goats per run, respectively) were exposed to varying phosphorus smoke concentrations for a period of 1 hour (59).

No deaths occurred among the mice during exposure at concentrations ranging from 110 mg/m^3 to 900 mg/m^3 except that in one of the runs 3 of 20 mice (15%) died during the 1-hr. exposure period at a concentration of 870 mg/m^3. The highest concentration of phosphorus smoke which did not cause death among the mice during one hour exposure was 900 mg/m^3. During the exposure period 5 of 20 mice (25%) died at a concentration of 1230 mg/m^3, 3 of 20 mice (15%) at 1510 mg/m^3 and 14 of 20 mice (70%) at the 1690 mg/m^3 concentration. Four of the mice died serially at 24 hours, 48 hours, 5 days and 10 days post-exposure at 110 mg/m^3 for 1 hr. At concentrations between 310 mg/m^3 and 660 mg/m^3, 6-10 of 20 mice (30-50%) succumbed in 24 hours to 10 days post exposure. More mice died from 24 hours to 10 days post exposure at concentrations ranging between 780 mg/m^3 and 1690 mg/m^3. The least concentration of phosphorus smoke inducing post exposure death in mice was 110 mg/m^3. Autopsy of the mice which died in the chamber revealed overall normal organs; the mice had died with wide-open mouths indicating the occurrence of death through respiratory causes. This found confirmation in the pathologic-anatomic findings of pulmonary congestion, atelectasis and possible emphysema in those mice which survived three to four days. Another constant observation was hemorrhaging in areas of the respiratory system. Occasional cloudy swelling of the heart, liver and kidney cells was also found (59).

In the rat studies, no deaths occurred during the one hour exposure from 380 mg/m^3 to 4800 mg/m^3 except for one rat (of 10) which died during this period at 4530 mg/m^3. From 24 hours to 48 hours post-exposure, no deaths occurred at concentrations of 380 mg/m^3 to 2150 mg/m^3 except in one run at 1350 mg/m^3 in which one rat (of 10) died during 24- and 48 hours post exposure. Five to 10 rats (50%-100%) died 1 to 10 days post exposure at concentrations of 4460 mg/m^3 to 4810 mg/m^3 with moderations of post exposure lethalities at concentrations of 2440 mg/m^3 to 4450 mg/m^3. The highest concentration of white phosphorus smoke which did not cause any death among the rats 24 hours post exposure was 1340 mg/m^3. The only remarkable autopsy findings in the rats which died from exposure regardless of the concentrations were those of pulmonary congestion, edema and occasional atelectasis. There were similar occurrences of cloudy cell swelling in livers and kidneys while other organs were unremarkable (59).

In the "brush" goats, no deaths occurred during exposure for one hour nor were there any up to 48 hours thereafter at concentrations of 540 mg/m^3 to 7310 mg/m^3. No deaths occurred in the 10 days after exposure at 540 mg/m^3 to 4810 mg/m^3. At concentrations of 6230 mg/m^3 to 7310 mg/m^3 there were 3-6 deaths out of 10 animals during days 5 to 10 after exposure. Greater numbers of goats died after 24 hours when exposed to concentrations ranging from 7750 mg/m^3 to 11470 mg/m^3. The highest concentration of phosphorus smoke which did not cause death among the goats was 4810 mg/m^3. Autopsy findings were edema, atelectasis and pneumonia. Most damage to the lung appeared 12 to 72 hours after exposure. Congestion and cloudy cell swelling were found in the livers and kidneys (59). The inhalation toxicity in animals is summarized in Table 17.

TABLE 16

INHALATION TOXICITY OF WHITE PHOSPHORUS SMOKE IN HUMANS

Number of subjects	Concentration of white phosphorus smoke (mg/m^3)	Length of exposure (minutes)	Effects observed
108	1000	not specified	Intolerable
108	700	not specified	Minimum harassing concentration
Not specified	592 588	3.5 2	Respiratory distress, nasal discharge, coughing, throat irritation and soreness
7	514	16	Nose and throat irritation, coughing during exposure
6	453	10	5/6 subjects showed throat irritation. One of these 5 subjects experienced nausea and nasal discharge during 3 days post exposure.
6	425	15	Nose and throat irritation during exposure but no remarkable effects during 3 days post exposure.
5	408	10	4/5 subjects had throat irritation and coughing. One subject experienced sore throat and symptoms of cold during 3 days post exposure.
7	188	5	5/7 experienced throat irritation, coughing and slight headache during exposure. Twenty four hours later, 4 subjects had frontal headache, nasal congestion, throat irritation and coughing. After 2 and 3 days only one subject showed signs of respiratory irritation.

TABLE 17

INHALATION TOXICITY OF WHITE PHOSPHORUS SMOKE IN ANIMALS AFTER ONE HOUR EXPOSURE

Species	Concentration of Smoke (mg/m^3)	Effects Observed
Mice	110	No deaths during exposure; 4/20 animals died 24 hours, 48 hours, 5 days, and 10 days post exposure, respectively.
	900	No deaths during exposure. Some animals died 24 hours to 10 days post exposure.
	1230	5/20 animals died during exposure; more deaths 24 hours to 10 days post exposure.
	1510	3/20 animals died during exposure; more deaths 24 hours to 10 days post exposure.
	1690	14/20 animals died during exposure; more deaths 24 hours to 10 days post exposure.
		Death in all cases due to respiratory failure. Other effects observed were hemorrhage in the lungs and occasional cloudy swelling of the heart, liver and kidney cells.
Rats	380-4800	No deaths during exposure except one (out of 10) which died at 4530 mg/m^3.
	380-2150	No deaths during exposure; only one death at 1350 mg/m^3 during 24-48 hours post exposure.
	4460-4810	5-10 (out of 10) died 1-10 days post exposure.
		Autopsy findings showed pulmonary congestion, edema, occasional atelectasis and cloudy swelling of the liver and kidney cells.
Goats	540-4810	No deaths during the exposure or up to 10 days post exposure.
	540-7310	No deaths during the exposure or up to 48 hours post exposure.
	6230-7310	16-66% deaths 5 to 10 days post exposure.
	7750-11470	Some deaths 24 hours post exposure.
		Autopsy findings showed pulmonary edema, atelectasis and pneumonia. Congestion and cloudy cell swelling were found in the liver and kidneys.

XIV. CARCINOGENICITY, MUTAGENICITY, AND TERATOGENICITY OF WHITE PHOSPHORUS

White phosphorus does not appear to be carcinogenic in experimental animals. Rats given oral doses of white phosphorus up to 1.6 mg/kg body weight daily for 512 days did not show any tumors (50,61). Subcutaneous injections of up to 3.2 mg/kg body weight given twice a week for more than 610 days did not cause any tumors in rats (61). No tumors were produced when dogs were given subcutaneous injections of 1 mg/kg white phosphorus in peanut oil daily for over 55 days (39). It should be emphasized, however, that these studies were not directed specifically towards carcinogenicity.

There have been no reported cases of carcinogenicity due to white phosphorus exposure in humans.

There are no studies available regarding the possible mutagenic or teratogenic potential in living systems.

XV. PHARMACOKINETICS OF WHITE PHOSPHORUS

The absorption, distribution, metabolism and excretion of white phosphorus have been explained by animal studies through the use of radioactive (^{32}P) white phosphorus. The results are described as follows.

A. ABSORPTION AND DISTRIBUTION

In humans white phosphorus can be absorbed through the skin, by ingestion, and through the respiratory tract. Occupational exposures primarily involve the inhalation route (26). In mice, rats and rabbits white phosphorus was moderately absorbed after oral administration (33,62). Cameron and Patrick (62) studied the distribution of white phosphorus after oral administration of radioactive phosphorus (^{32}P) in mice, rats and rabbits. The animals were given the following single doses of ^{32}P in arachis oil: mice 0.5 mg, rats 3.5 mg, and rabbits 20.0 mg. The radioactivity per dose was 0.1 millicurie, 0.35 millicurie, and 1.0 millicurie, respectively. Animals were killed after 48 hours and specimens of most organs and tissues were obtained. The average concentrations of radioactivity in the tissue homogenates determined 48 hours after the administration of the doses are given in Table 18.

In female rats (number not specified) given single oral doses of 0.3 mg/kg body weight of ^{32}P-labeled white phosphorus, about 60-65% of the dose was absorbed and the absorption was essentially completed in 24 hours. The liver contained the highest amount of radioactivity, representing 16.1% of the dose at 4 hours, 16.9% at 1 day, and 6.3% at 5 days. Radioactivity in the blood represented 6.1%, 4.1%, and 1.7% of the administered dose at the end of 4 hours, 1 day, and 5 days, respectively. The amount in the muscle, averaging 4.0%, 5.5%, and 6.0% at 4 hours, 1 day, and 5 days, respectively, was probably due to the large mass of muscle in the body. The amount of radioactivity remaining in the gastrointestinal tract was 57%, 15.3%, and 1.7% of the administered dose at the end of 4 hours, 1 day, and 5 days respectively (33). Table 19 summarizes the distribution of radioactivity in rats receiving ^{32}P-labeled white phosphorus. The distribution of radioactivity in the various tissues, relative to plasma, 4 hours after administration of the label was in the following order: liver > kidneys > lungs > spleen > bone > muscle > brain. These ratios are summarized in Table 20. The radioactivity concentration in the blood decreased slowly and consistently; whereas the radioactivity in various tissues remained high or decreased only slightly. This resulted in large increases in the tissue to plasma radioactivity ratios in all tissues (33).

Another group of female rats (number of animals not given) was dosed with ^{32}P-labeled white phosphorus for 5 consecutive days (0.3 mg/kg body weight daily). The amount of radioactivity in each tissue 24 hours after the last dose was compared with that in the tissue 24 hours after a single dose. The results are summarized in Table 21. All the tissues from rats receiving 5 daily doses contained 4.1 to 10.5 times as much radioactivity as those receiving a single dose, indicating an accumulation of radioactivity in all tissues (33). Distribution in the tissues of rats after administration of radioactive ^{32}P white phosphorus has also been studied by Ghoshal et al (63). Rats were given ^{32}P mixed with 7.5 mg/kg of body weight of unlabeled white phosphorus in mineral oil following gastric intubation. White phosphorus was rapidly absorbed and was mainly incorporated into the liver where it reached its maximum (69-73%

TABLE 18

THE AVERAGE RADIOACTIVITY (millimicrocuries per milligram tissue) IN THE TISSUE HOMOGENATES 48 HOURS AFTER A SINGLE ORAL ADMINISTRATION OF ^{32}P WHITE PHOSPHORUS

TISSUE	MICE	RATS	RABBITS
Blood/ml	57.0	20.0	50.0
Liver	0.2	0.16	0.1
Kidney	0.18	0.12	0.06
Spleen	0.18	0.1	0.06
Lung	0.16	0.06	0.05
Heart	0.05	0.06	0.02
Muscle	0.05	0.05	0.02
Pancreas	0.05	0.04	0.01
Adrenal	0.05	0.01	0.023
Brain	0.03	0.02	0.02
Thymus	0.03	0.01	0.02
Fat	0.015	0.005	0.005

Ref: Cameron and Patrick (62)

TABLE 19

DISTRIBUTION OF RADIOACTIVITY IN RATS
RECEIVING ^{32}P WHITE PHOSPHORUS

	% of Administered Dose		
	4 Hours	1 Day	5 Days
Gastrointestinal Tract plus Contents	57.0 ± 3.4	15.3 ± 4.0	1.7 ± 0.2
Whole Blood (Based on 7.0% of the body weight)	6.1 ± 1.1	4.1 ± 0.5	1.7 ± 0.0
Liver	16.1 ± 4.6	16.9 ± 0.7	6.3 ± 0.3
Kidneys	0.7 ± 0.2	0.8 ± 0.1	0.4 ± 0.0
Spleen	0.1 ± 0.0	0.1 ± 0.0	0.1
Brain	0.1 ± 0.0	0.1	0.1
Lungs	0.4 ± 0.0	0.3 ± 0.1	0.2 ± 0.0
Skeletal Muscle (Based on 40% of the body weight)	4.0 ± 0.0	5.5 ± 0.2	6.0 ± 0.6
Recovery	98.6 ± 5.0	94.0 ± 3.3	96.0

Ref: Lee et al. (33)

TABLE 20

TISSUE/PLASMA RATIOS OF RADIOACTIVITY IN RATS RECEIVING A SINGLE DOSE OF ^{32}P WHITE PHOSPHORUS

TISSUE	TISSUE/PLASMA RADIOACTIVITY RATIO (Ratio of Radioactivity in 1 ml or 1 g of wet tissue to radioactivity in 1 ml of plasma)		
	4 Hours	1 Day	5 Days
Liver	18.7 ± 2.5	51.4 ± 3.9	103.2 ± 10.0
Kidneys	4.2 ± 1.0	14.4 ± 1.2	33.5 ± 4.1
Spleen	1.8 ± 0.4	6.4 ± 2.6	18.6 ± 2.6
Brain	0.3 ± 0.0	0.7 ± 0.0	3.6 ± 0.4
Skeletal Muscle	0.4 ± 0.0	1.8 ± 0.1	8.7 ± 0.5
Bone	1.7 ± 0.1	1.2 ± 0.1	66.9 ± 17.2

Ref: Lee et al. (33)

TABLE 21

ACCUMULATION OF RADIOACTIVITY IN RATS RECEIVING ^{32}P WHITE PHOSPHORUS

	^{32}P 24 Hours After A Single Dose (disintegration per minute /gx10^{-5})	^{32}P 24 Hours After the Last of 5 Daily Doses (disintegration per minute /gx10^{-5})	Ratio*
Blood	2.91	28.42	9.8
Liver	19.30	79.44	4.1
Kidney	5.44	39.29	7.2
Spleen	2.38	17.70	7.4
Brain	0.25	2.63	10.5
Lungs	2.18	22.21	10.2
Skeletal Muscle	0.68	5.90	8.7
Bone	4.77	38.81	7.7

* Ratio of radioactivity per gram of wet tissue from rats receiving 5 consecutive daily doses assayed 24 hours after the last dose to the radioactivity per gram of wet tissue from rats receiving a single dose assayed 24 hours after dosing.

Ref: Lee et al. (33)

of the given dose) within 2-3 hours. At the moment of maximum hepatic incorporation (2 hours), the percentages of the given dose recovered from blood (12%), kidneys (4%), spleen (0.4%), pancreas (0.4%), and brain (0.39%) were significantly lower than that of liver (65%) ($p<0.001$ for all comparisons). Fifty four percent of the total hepatic isotope was present in the supernatant fraction and the rest almost equally distributed among the other subcellular fractions (63).

In a study geared to estimating the uptake of ^{32}P (as carrier-free ^{32}P as supplied by the Atomic Energy Research Establishment, Harwell, England) by the skin, 36 Agouti and Chinchilla rabbits of both sexes weighing about 2 kg were given 75 microcurie ^{32}P/kg intravenously. The animals were then sacrificed at intervals under Nembutal. The radioactivity of the skin of the trunk including the panniculus carnosus was then determined in an M6 liquid counter. It was found that in the rabbits killed 5 minutes after ^{32}P administration, much larger amounts of the isotope were taken up in growing areas of the skin than in quiescent areas. Identical observations were made in those animals killed after 24 hours and after 72 hours. The study indicated that the uptake of ^{32}P by rabbit skin was dependent upon the physiologic state (64).

B. METABOLISM

White phosphorus is metabolized in the body (human and animals). Urinary metabolites include organic and inorganic phosphates (33, 26). Although it would appear by the above studies that phosphorus is rapidly converted to phosphate the site or sites of oxidation has not been determined.

C. EXCRETION

In humans white phosphorus is excreted chiefly in the urine as organic and inorganic phosphates. Insignificant amounts of unchanged white phosphorus may be excreted in the exhaled breath, sweat, and feces (26). In rats the excretion occurs mainly through urine in the form of organic and inorganic phosphates. Rats given single oral doses of 0.3 mg/kg body weight of ^{32}P white phosphorus excreted the majority of the absorbed radioactivity in the urine, averaging 17.1% of the administered dose at 4 hours, 34.5% at 1 day, and 46.7% at 5 days. During these same time periods, some radioactivity was also recovered in the feces. Radioactivity averaging 2.0%, 16.6%, and 33% of the administered dose was recovered from the feces at 4 hours, 1 day, and 5 days, respectively (33).

XVI. BIOCHEMICAL CHANGES IN LIVER AND BLOOD

Biochemical changes have been studied in experimental animals. The major changes occur in the liver and blood and are described as follows.

Acute phosphorous toxicity-induced biochemical changes in the liver were studied by Truhaut et al. (65) in fifty 5-month old Wistar rats weighing about 386 g. The animals were divided into two groups of 25 rats per group of which 10 were controls. In Group one, 15 rats received, subcutaneously, 2.5 mg/kg body weight white phosphorus in olive oil every 2 or 3 days. A total of 10 injections of 25 mg/kg was administered to each rat. In Group two, 15 rats received, subcutaneously, 5 mg/kg body weight white phosphorus in olive oil every 2 or 3 days with the treatment repeated giving a total of 15 mg/kg per rat. Three rats died in Group 1 after the ninth injection (25 days after initiation of treatment) while in Group 2, 4 rats died after the third injection (7 days after initiation of treatment). Treatment of the 20 control rats was not indicated in the report. All surviving rats were killed two days after the last injection (day 28 in Group 1 and day 8 in Group 2).

Blood and livers were sampled for assessments of hepatic tissue enzyme activity and serum and hepatic lipid fractions. After a total dose of 2.5 mg/kg body weight, there was a significant ($p<0.01$) increase in hepatic triglycerides and decrease in hepatic phospholipids ($p<0.01$) when compared to the controls. However, total hepatic lipids and total hepatic cholesterol did not show significant variations from normal values. At 5 mg/kg there was a highly significant increase in triglycerides ($p<0.001$) but the elevation of total lipids as compared to controls was not significant ($p<0.2$). There was a slight decrease in the phospholipids after treatment. Total cholesterol was not determined in this group. The effect of the two doses (2.5 mg/kg body weight and 5 mg/kg body weight)on the tissue enzymes was comparable. There was a highly significant decrease in fructose 1,6 diphosphate aldolase (F16D) when compared to controls ($p<0.001$). While there was a significant decrease in malic dehydrogenase ($p<0.02$) at 2.5 mg/kg body weight, the toxicity due to 5 mg/kg did not show any appreciable change. Total serum lipids were not affected at 2.5 mg/kg but there was a highly significant decrease in triglycerides ($p<0.001$) when compared to controls. Doses of 5 mg/kg white phosphorus increased total serum cholesterol, although the difference was not significant ($p>0.05$). The experimental results are depicted in Table 22.

Truhaut et al. (66) followed up their previous study of the biochemical changes in the liver caused by repeated injections of white phosphorus by studying the acute toxicity following a single dose. Thirty-three 5 1/2 month old male Wistar rats were given 10 mg/kg body weight white phosphorus in olive oil subcutaneously. The number of rats comprising the controls was not indicated. Two of the 33 rats died in less than 24 hours, 7 died between 24 and 48 hours and 1 died between 48 and 72 hours after the injection. Surviving rats were killed 18, 24, 36, 48, 72 and 96 hours respectively post injection.

The weight of the liver, as compared to controls, was significantly increased throughout from 18 to 96 hours post injection. (See Table 23). Up to 18 hours there was no significant change in the total lipid content of the liver as compared to controls; thereafter, however, the value increased significantly. The increase was clearly appreciable when the total liver content was considered. Triglycerides showed a significant increase from 18 hours onwards. Total hepatic cholesterol increases were significant ($p<0.02$) only in rats killed after

TABLE 22

LIPID AND ENZYME LEVELS IN RATS AFTER SUBCUTANEOUS ADMINISTRATION OF WHITE PHOSPHORUS

Effect on Weight of Liver		2.5 mg/kg body weight		5 mg/kg body weight	
		Controls	Poisoned	Controls	Poisoned
	Liver Weight (g)	13.3 ± 1.0	10.1 ± 1.6	11.1 ± 2.1	11.6 ± 2.1
Effect on hepatic lipids (mg/g of liver tissue)	Total Lipids	31.4 ± 0.7	30.3 ± 3.4	29.0 ± 7.5	36.9 ± 4.8(110)+
	Triglycerides	3.8 ± 0.7	9.5 ± 3.1	2.7 ± 1.1	12.7 ± 1.7(73.5)
	Total Cholesterol	2.0 ± 0.4	2.4 ± 0.6	--	--
	Phospholipids	22.3 ± 1.2	14.8 ± 3.6	24.5 ± 3.9	20.3 ± 2.1(20.5)
Effect on hepatic enzymes (International Units/g of protein)	G6PD	11.8 ± 3.7	11.1 ± 0.6	11.8 ± 3.7	10.3 ± 0.8
	*LDH	630 ± 183	500 ± 94	790 ± 91	823 ± 326
	*MDH	1852 ± 68	1288 ± 127	1480 ± 176	1225 ± 358
	*F16D	13.1 ± 0.8	6.0 ± 0.9	13.8 ± 1.3	10.5 ± 1.8
Action on serum lipids (g/l)	Total Lipids	2.88 ± 0.24	2.50 ± 0.12	2.68 ± 0.40	3.02 ± 1.10
	Triglycerides	1.38 ± 0.19	0.64 ± 0.07	0.91 ± 0.27	0.82 ± 0.19
	Total Cholesterol	0.66 ± 0.13	0.70 ± 0.09	0.66 ± 0.08	0.91 ± 0.13
	Phospholipids	0.69 ± 0.16	0.82 ± 0.25	0.82 ± 0.53	1.00 ± 0.34

Ref: Truhaut et al. (65).

* LDH = Lactic dehydrogenase
MDH = Malic dehydrogenase
F16D = Fructose 1,6 diphosphate aldolase
G6PD = Glucose-6-phosphate dehydrogenase

+ Numbers in parentheses are values derived from rats which had severe hepatic steatosis (2 rats).

TABLE 23

ACTION OF WHITE PHOSPHORUS (10 mg/kg) ON
LIVER WEIGHT AND HEPATIC LIPIDS IN RATS

Time Killed (Hours After Poisoning)		Liver Weight (g)	Hepatic Lipids							
			Total Lipids		Triglycerides		Total Cholesterol		Phospholipids	
			mg/g	mg/liver	mg/g	mg/liver	mg/g	mg/liver	mg/g	mg/liver
Controls	m	10.8	47.9	512	9.17	99.8	3.06	32.7	30.1	323
	s	1.2	4.3	55	368	44.5	0.53	5.0	3.8	41
	m	13.9	47.1	658	19.50	273	2.34	32.7	24.6	343
18	s	0.5	4.1	77	5.1	78	0.16	2.6	1.6	22
	p	<0.001	NS	<0.001	<0.001	<0.001	<0.02	NS	<0.01	NS
	m	15.4	85.2	1312	37.5	576	3.22	49.7	33.1	511
24	s	0.7	11.5	167	6.2	82	0.29	4.6	2.6	54
	p	< 0.001	<0.001	<0.001	<0.001	<0.001	NS	<0.001	NS	<0.001
	m	15.2	91.9	1395	51.2	797	4.21	63.6	31.8	479
36	s	0.6	3.5	98	12.5	250	1.10	14.8	3.5	114
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.02	<0.001	NS	<0.001
	m	15.6	109	1700	57.2	893	3.72	57.9	39.7	621
48	s	0.7	17	283	13.7	216	0.43	4.8	3.9	75
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.02	<0.001	<0.001	<0.001
72	m	16.2	110	1809	65.9	1094	3.45	54.9	29.3	472
96	m	16.1	119	1910	71.8	1151	5.12	82.0	24.7	395

Ref. Truhaut et al. (66).
m = Mean of arithmetic values
s = Deviation
p = Level of significance
NS = Not significant

18,36 and 48 hours. Significant hepatic phospholipid increases were only observed after 18 hours ($p<0.01$) and after 48 hours ($p<0.001$). Variations noted at other periods were not significant.

Glucose-6-phosphate dehydrogenase (G6PD) did not change significantly after 18, 24 and 48 hours. There was a significant increase ($p<0.05$) in G6PD at 36 hours post injection when compared to the controls. There was no appreciable variation in the lactic dehydrogenase (LDH) values until 48 hours after injection when there was a significant decrease ($p<0.05$). The only modification observed in the malic dehydrogenase values was at 18 hours post injection when a highly significant ($p<0.001$) increase was noted. At 48 hours after injection a significant ($p<0.05$) decrease was observed in the aldolase when compared to controls (see Table 24).

In serum, total lipids, triglycerides and total cholesterol decreased after administration of white phosphorus (see Table 25) except at 18 hours after injection when there was no significant difference in triglycerides between controls and treated rats. Serum phospholipids were decreased significantly ($p<0.01$-0.001) at 18, 24 and 36 hours after injection, but did not differ significantly from controls at 48 hours.

Serological studies performed in rabbits after administration of 0.1, 1.0, and 2.0 mg/kg body weight of white phosphorus showed all groups to have increased non-protein nitrogen, amino acid nitrogen, uric acid and slight increases in creatine and creatinine (67). In phosphorus intoxicated rabbits, serum studies showed increased alpha- and beta-globulins but no increase in serum glucosamine in comparison with sera from unexposed animals (67).

Thirty six male Wistar rats weighing 160 to 200 gm were divided into two groups. One group received by gastric intubation 7.5 mg/kg body weight of white phosphorus in mineral oil. Rats in the other group (the controls) received the equivalent amount of mineral oil alone. A number of rats from each group were decapitated at 4, 12 and 24 hours after intoxication and their livers were removed for assessment of G-6-Phosphatase activity in the microsomes. There was no significant difference in G-6-phosphatase activity between controls and treated rats after 4 hours. However at 12 and 24 hours post-intoxication significant ($p<0.025$ and $p<0.01$ respectively) increases in activity were noted as compared to controls; see Table 26 (63).

Fleming and Collins (43) studied the chylomicron count in the blood of rats given subcutaneous injections of white phosphorus (1.1 mg/kg body weight) in peanut oil. No significant changes occurred in fasting rats but significant and reproducible changes were noted 4 hours after resuming food intake.

An increase in blood guanidine was observed in dogs following phosphorous administration (conditions of the experimental study were not elaborated upon). The study indicated that the guanidine increase was probably due to liver damage. Hypoglycemia was also observed (67).

Bueding and Ladewig (40) found that the glucuronic acid produced by liver slices from guinea pigs which survived subcutaneous injections of 0.75 mg/kg body weight in olive oil was considerably reduced (see Table 27).

TABLE 24

ACTION OF WHITE PHOSPHORUS (10 MG/KG) ON HEPATIC ENZYMES IN THE RAT

Time Killed (Hours After Poisoning)		Hepatic Enzymes (1 U/g)*			
		G6PD	LDH	MDH	F16D
Controls	m	9.72	618	1196	11.86
	s	4.05	296	316	3.24
	m	9.14	542	1916	13.32
18	s	2.58	104	183	1.39
	p	NS	NS	<0.001	NS
	m	5.29	547	893	10.01
24	s	0.65	54	158	1.08
	p	NS	NS	NS	NS
	m	16.64	640	1479	12.47
36	s	6.75	283	578	2.48
	p	<0.05	NS	NS	NS
	m	11.19	261	1031	8.97
48	s	3.15	78	113	0.69
	p	NS	<0.05		<0.05
72	m	5.56	345	535	4.40
96	m	3.78	451	542	5.23

Ref : Truhaut et al. (66).

* 1 U/g = International Units per gram of protein

G6PD = Glucose-6-phosphate dehydrogenase
LDH = Lactic dehydrogenase
MDH = Malic dehydrogenase
F16D - Fructose 1,6 diphosphate aldolase
m = Mean of arithmetic values
s = Deviation
p = Level of Significance
NS = Not significant

TABLE 25

ACTION OF WHITE PHOSPHORUS (10 MG/KG) ON SERUM LIPIDS IN THE RAT

Time Killed (Hours after Poisoning)		Serum Lipids (g/l)			
		Total Lipids	Triglycerides	Total Cholesterol	Phospholipids
Controls	m	3.05	0.73	0.66	1.34
	s	0.60	0.12	0.19	0.33
	m	2.24	0.71	0.39	0.75
18	s	0.33	0.34	0.07	0.24
	p	<0.01	NS	<0.01	<0.01
	m	1.25	0.33	0.21	0.42
24	s	0.33	0.07	0.04	0.21
	p	<0.001	<0.001	<0.001	<0.001
	m	1.03	0.30	0.17	0.42
36	s	0	0.01	0.06	0.31
	p	<0	<0.001	<0.001	<0.01
	m	1.67	0.36	0.36	1.09
48	s	0.60	0.08	0.14	0.42
	p	<0.001	<0.001	<0.01	NS
72	m	3.68	0.45	1.08	Insufficient
96	m	3.35	0.52	1.05	Samples

Ref: Truhaut et al. (66)
m = Mean of arithmetic values
s = Deviation
p = Level of Significance
NS = Not significant

TABLE 26

ACTIVITIES OF HEPATIC GLUCOSE-6-PHOSPHATASE AT DIFFERENT PERIODS IN CONTROL AND PHOSPHORUS-INTOXICATED (7.5 MG/KG) RATS*

Hours	Control	Phosphorus	p values
4	3.92 ± 0.36	3.42 ± 0.25	N.S.
12	3.98 ± 0.26	5.15 ± 0.26	<0.025
24	2.98 ± 0.15	4.15 ± 0.22	<0.001

Ref : Ghoshal et al. (63).

* Values are given in mg of P split from glucose-6-phosphatase in 20 minutes at 30°C per equivalent gram of microsomes. Each figure represents the mean ± s.e. from 6 rats.

NS = Not significant

TABLE 27

LIVER SLICES OF GUINEA PIGS INTOXICATED WITH PHOSPHORUS

		Milligrams of glucuronic acid produced by 1 g of dried liver	
		Saline containing 0.01% borneol	Saline containing 0.01% borneol and 0.02M lactate
20 normal controls	Limits	1.1-5.4	1.7-11.4
	average	2.85	5.05
	increase		+ 77%
10 guinea pigs intoxicated with phosphorus 0.75 mg/kg body weight	Limits	0.25-3.8	0.25-4.9
	Average	1.8	2.0
	Increase		(+ 11%)

Ref: Bueding and Ladewig (40).

XVII. INDUSTRIAL HYGIENE AND SAFETY PRACTICES FOR WHITE PHOSPHORUS

Prevention of systemic intoxication among workers occupationally exposed to white phosphorus depends mainly upon engineering controls and medical surveillance. This section provides information on handling, transportation, storage, preventive measures in industry, fire hazards, and medical control.

1. MATERIALS OF CONSTRUCTION FOR CONTAINERS

Because white phosphorus ignites spontaneously in the presence of air, it is stored under water. Under water white phosphorus may react with dissolved oxygen to form phosphoric acid, which may eventually corrode the container. Therefore the normal material of construction for the containers should be stainless steel (68).

2. TRANSPORT, HANDLING AND STORAGE

White phosphorus is normally supplied in sealed containers under sufficient water. All containers should be transported and stored in the upright position and must be allowed free movement on the carrying vehicles, thereby preventing physical damage to the containers. Containers should be transported and stored in single stacks in order to limit the degree of involvement of other containers, and also to facilitate remedial measures to be taken in case of damage. Rupture of the container creates an insidious hazard leading to loss of water, exposure to air and ignition of the white phosphorus. Ruptured drums should be isolated as speedily as possible and the loss of water should be stopped either by small wooden plugs or by placing the container in such a position as to prevent further loss of water. Wherever containers of white phosphorus are handled, adequate supplies of water should be readily available. The phosphorus containers should be stored in a cool, dry, and well ventilated place. These should be kept away from inflammable, combustible materials. Containers should be frequently examined for corrosion and leaks (68).

3. PREVENTIVE MEASURES IN INDUSTRIES

The engineering efforts in industries, either manufacturing or using white phosphorus, should be directed toward control of exposure to dust and fumes. Suitable local and general ventilation should be provided in work areas. The industry should be remote from houses and built of fireproof materials. Consumption of food and drinks in the work areas should be strictly prohibited. Careful washing of hands, rinsing of the mouth, and changing [illegible] should be practiced in order to avoid any contamination. [illegible]s should be strictly organized. The electrical installations should [illegible]ly safeguarded and periodically inspected (12). It is of utmost [illegible]rance that all employees concerned with handling and processing of white phosphorus be well trained in the safe and correct method of job procedures. They should know the immediate location of water showers, fire extinguishers, and safety blankets. Suitable gloves and eye protection should be worn. Hat, jacket and trousers of woolen material, knee length rubber boots and polyvinyl chloride aprons should also be worn. In case of accidents where large volumes of smoke arise from burning phosphorus, breathing apparatus and gas masks should be readily available (68).

4. FIRE HAZARDS AND CONTROL

Phosphorus ignites spontaneously upon exposure to air. In the exposed solid form it ignites and burns slowly at first, but combustion will intensify rapidly as heat converts the solid to liquid phosphorus. Leakages of molten phosphorus can flow as liquid fire and the burning liquid can spread.

Fire of white phosphorus can be controlled with water, sand, or similar materials which exclude air. The objective is to solidify any molten phosphorus and to maintain a water film on the solid phosphorus. Steady, low pressure volumes of water are required. High pressure can spread phosphorus and increase the area of fire. Where considerable quantities of phosphorus are on fire it may be necessary to form a dam or seal the fire area with sand bags, so that the burning phosphorus can be submerged under water (68).

5. MEDICAL SURVEILLANCE

Medical control, for prevention of systemic intoxication, should start with the pre-employment medical examination including x-ray studies of the teeth and jaw. No one should be permitted to be employed unless his dentition is excellent. Periodic physical examinations should be directed, again, to the mouth and should include dental x-rays. Routine dental examination should be made monthly. Extraction of the teeth and fillings should be followed by two months exclusion of the affected worker from the work areas. At the least suspicion of jaw injury, the worker should be removed from the areas of potential exposure (11, 31, 69).

XVIII. STANDARDS FOR WHITE PHOSPHORUS

The Occupational Safety and Health Administration (OSHA) of the United States Department of Labor has set the limiting concentration of 0.1 mg/m^3 in air for white phosphorus. The standards set for phosphoric acid and phosphine are 1.0 mg/m^3 and 0.4 mg/m^3, respectively. These standards are 8-hour time-weighted averages not to be exceeded in any 8-hour shift of a 40-hour work week (70). A threshold limit value of 1 mg/m^3 has been recommended by the American Industrial Hygiene Association for occupational exposure to phosphorus pentoxide (8-hour time-weighted average) (100).

XIX. SAMPLING AND ANALYSIS OF PHOSPHORUS

From the analytical point of view much concern has developed over the estimation of white phosphorus in recent years. Due to its apparent low toxicity, investigation of the qualitative and quantitative determination of red phosphorus has not been carried out by analytical chemists. Following is an overview of the methods available for sampling procedures and analytical techniques for white phosphorus. The emphasis has been on recent developments of analytical methods and only papers appearing after 1965 have been included. The methodology covered in this report has been limited to samples in air and biological media. There are no reports in the literature dealing with sampling and analysis of plasticized white phosphorus, epoxy white phosphorus, butyl rubber/red phosphorus, or smokes generated from these compounds. Since there are reports confirming the fact that, upon burning, white phosphorus produces phosphorus pentoxide as the major component of smoke which, in the presence of moisture is converted to phosphoric acid, procedures available for sampling and analysis of these chemicals have also been included, when available. Techniques reported in the literature for the analysis of phosphine have also been briefly mentioned.

A. AIR SAMPLING METHODS

1. WHITE PHOSPHORUS

One of the problems in phosphorus determination is separating free phosphorus from the many phosphorus compounds found in air. A method developed by Rushing (71) consists of drawing air samples through an impinger containing 100 ml of xylene at a rate of 0.028 cubic meters per minute for fifteen minutes. A small circle of Whatman No. 41 filter paper is attached in a convenient holder on the exit side of the impinger to catch any fumes which pass through xylene. Another method employs collecting the sample on 20 x 25 cm fiber glass filter papers (72). Arato-Sugar (73) passed the air sample through an oxidizing mixture containing 0.025N potassium permanganate and 0.05N sulfuric acid. A similar sampling method has been described in which air is passed at a flow rate of 100 liters per hour through a moist filter paper placed on a filter with a sintered glass disc (74). A solution of 2.5N sodium hydroxide or 1:1 mixture of 2.5N sodium hydroxide and methyl cellosolve (2-methoxyethanol) has also been used to absorb phosphorus from air (75).

2. PHOSPHORUS PENTOXIDE

Samples of air containing phosphorus pentoxide can be collected by the method described by Rushing (71) for white phosphorus, in which air is passed through an impinger containing xylene. The xylene solution can then be treated with oxidant-free water (prepared by distilling from hydrazine sulfate) to transfer phosphorus pentoxide to the aqueous layer.

3. PHOSPHORIC ACID

Sampling of phosphoric acid mist in air can be accomplished by a method used for particulate sampling (76). The sampling set up consists of a probe, cyclone, filter, four impingers, pump, dry-gas meter, calibrated orifice, and a manometer, in the order listed. The cyclone is designed so that particulate samples can be separated into two fractions.

diameter less, and the other having particles greater than 5 microns. The first two impingers contain water, the third one is dry, and the fourth contains silica gel. When phosphoric acid mist is sampled, the fritted-glass and paper filters are removed, so that all particles passing through the cyclone are collected in the impingers.

4. PHOSPHINE

Air samples for analysis of phosphine are collected at a rate of 0.5 liter per minute (for about 10 minutes) in a fritted-glass bubbler. The bubbler contains silver diethyldithiocarbamate and has a collection efficiency of 86.2% at the rate of 0.5 liter per minute and 75% at the rate of one liter per minute (77).

B. BIOLOGICAL MEDIA SAMPLING METHODS

Samples of tissue (up to 10 g) are homogenized for 2 minutes with 50 ml of organic extractant (either benzene or iso-octane) in a stainless steel blender (Sorvall "Omnimixer") cooled in ice. The blend is filtered and the residue re-extracted if necessary. The filtrate is allowed to separate and the organic layer is used for analysis (78). A recent method involving neutron activation analysis uses a sample in which elemental phosphorus in the tissue samples is converted to silver phosphate (79). The ground tissue sample is washed. A stream of nitrogen is passed through the sample for 30 minutes. The mixture is then acidified and liberated phosphine is passed through lead acetate and is absorbed by glass wool (presoaked in methanolic silver nitrate) and dried. The phosphine trapped on the glass wool by the formation of black silver phosphide is oxidized to white silver phosphate by exposing it to chlorine vapor.

A method for sampling of saliva and mineralized dental tissue (dentine) has been reported by Retief et al. (80). Saliva is centrifuged at 3,000 revolutions per minute for ten minutes to remove the epithelial cells and suspended matter. The centrifuged saliva is filtered through Whatman No. 1 filter paper and the filtrate is utilized for analysis. Dentine is ground to a fine powder in an agate mortar and dried to constant weight at 105°C. The dentine is then dissolved either in 1.0 N hydrochloric acid or 0.8 M trichloroacetic acid, or ashed. For the determination of phosphorus in blood and urine, the samples are heated with a mixture of 57% perchloric acid and 57% nitric acid (1:2) and then converted to the phosphomolybdate complex (81).

C. ANALYSIS

1. WHITE PHOSPHORUS

A rapid, sensitive and specific method for the determination of elemental phosphorus in air has been described by Bohl and Kaelble (82). The phosphorus in a measured volume of air is collected in xylene, and a portion (6 µl) of xylene solution is injected into a gas chromatograph equipped with a flame photometric detector. Separation is accomplished on a 182.9 x 0.6 cm U-shaped glass column packed with 3.8% SE-30 silicone gum rubber on 80-100 mesh Chromosob W. The column temperature is about 80°C. The detection limit is 0.4 µg/m³ of air. The reproducibility of the method is reported to be ± 0.003 mg/m³ at 95% confidence. The same technique has been used to

determine white phosphorus in biological samples. Phosphorus levels as low as 1.0 picogram (10^{-12} g) can be measured by this method (78, 83, 84).

A flame emission photometer has been used to determine white phosphorus in air with a detection limit of 3.0 ng/m^3 (85).

Recently, neutron activation analysis has been reported to determine white phosphorus in air and in biological samples, by using a neutron flux of 10^9 neutrons/cm^2-sec and an irradiation time of 5 minutes. Concentrations of phosphorus in nanograms can be detected (72, 79).

A number of colorimetric methods have also been employed for the estimation of white phosphorus in air and in biological samples (71, 74, 80, 81, 86), most of which are based upon the conversion of phosphorus to phosphate which is then treated with ammonium molybdate to form a colored complex. The colors are compared with standards by a spectrophotometer using a wavelength of 720 nm. About 1-2 µg of phosphorus can be measured.

2. PHOSPHORIC PENTOXIDE

There are no direct instrumental methods available for the determination of phosphorus pentoxide. Indirect methods that can be used for its detection include conversion to phosphoric acid and phosphates, which can be determined by either colorimetry or gas chromatography. These methods are described under phosphoric acid.

3. PHOSPHORIC ACID

Methods of chemical analysis of oxygen-containing acids of phosphorus have been reviewed by Ohashi (87). Butts (88) and Addison (89) have employed a gas chromatographic technique utilizing a flame ionization detector for the estimation of oxyacids of phosphorus based on formation of trimethylsilyl derivatives. A borosilicate glass column (366 x 0.6 cm) packed with 3% OV-17 on 90-100 mesh Gas Chrom Q is used. The inlet and detector temperature are approximately 250°C.

Aqueous solutions of phosphoric acid can be determined by titration with permanganate or other oxidant (71).

Determination of phosphoric acid emitted from stacks of phosphoric acid plants has been accomplished by a colorimetric method, which is based on the spectrophotometric determination of the yellow ammonium phosphomolybdovandate complex formed when orthophosphate reacts with the agent in an acidic medium. This method is applicable to the detection of total phosphates in the concentration range of about 50 µg to 2 mg, with a replication precision of ± 1.0% (76). Another colorimetric method for estimation of phosphoric acid in air has been described by the National Institute for Occupational Safety and Health (90), in which the sample is treated with sodium molybdate and hydrazine sulfate to form a blue complex. The absorbance of the resulting solution is determined at 830 nm. Levels of phosphoric acid in the range of 0.47-1.93 mg/m^3 can be detected by this method.

4. PHOSPHINE

Phosphine in air and in biological samples has been determined by gas chromatography using a flame photometric (phosphorus mode) detector (91). A stainless steel column (46 x 0.6 cm) packed with 3% Carbowax 20M on 60-80 mesh Gas Chrom Q is employed at a column temperature of 65°C. The detection limit is 5 picograms (5×10^{-12} g) of phosphine.

Phosphine in air has also been determined by a spectrographic method, which depends on the formation of a complex of phosphine with silver diethyldithiocarbamate with an absorption maximum at 465 nm. Concentrations in the range of 0.13-1.3 mg/m^3 of air can be determined (77).

5. TOTAL PHOSPHORUS

In addition to the analytical techniques mentioned above there are some spectrometric methods which can determine phosphorus quantitatively and are reviewed by Kaelble (92). These methods are not specific for white phosphorus, phosphine or phosphoric acid but determine the total amount of phosphorus in a sample, which may include organophosphorus compounds as well. Among these methods are x-ray spectroscopy capable of detecting nanogram levels, emission spectroscopy with a detection limit of 2 mg/kg of biological materials including animal tissue, blood serum, feces, and bone. Spark source mass spectrometry with sensitivity limits in nanograms is especially advantageous since it uses very small amounts of sample.

XX. BUTYL RUBBER/RED PHOSPHORUS SMOKE COMPOUND

Butyl rubber/red phosphorus smoke compound is prepared by mixing about 75% of red phosphorus with about 2-6% of styrene-butadiene rubber (plasticizer) in 20-30% of a solvent such as gasoline, xylene or naphtha. No special precaution nor special skill is necessary in preparing the butyl rubber/red phosphorus. The resulting mixture has a jelly-like consistency and is readily ignited with a match to produce a good screening smoke (10). The United States military specifications for red phosphorus and styrene-butadiene rubber are given in Tables 28 and 29, respectively.

No information is available relating to human toxicity, epidemiology, animal toxicity, metabolism or industrial hygiene and standards of butyl rubber/red phosphorus. See sections V-X for a discussion of red phosphorus.

There is one report on toxicity of pyrolysis products of styrene-butadiene rubber (93). Four Swiss albino male mice were exposed to pyrolysis products of styrene-butadiene rubber. One gram of the rubber was pyrolyzed by heating from 200-800°C at a heating rate of 40°C/minute in a he[illegible]spherical chamber of 4.2 liter capacity. The mice staggered after 11 minutes, convulsed, and collapsed after 20 minutes, and died after about 23 minutes. Analysis of the gases in the chamber gave oxygen (221,000 mg/m^3), carbon dioxide (72,000 mg/m^3), carbon monoxide. (11,495 mg/m^3), methane (2,027 mg/m^3), and ethylene (960 mg/m^3). The principal cause of death was carbon monoxide poisoning. This was evident from analysis of blood which showed 96% carboxyhemoglobin.

It should be pointed out that the levels of these gases would be different when styrene-butadiene rubber is burned in air since the excess of atmospheric oxygen will reduce the concentration of carbon monoxide.

TABLE 28

U.S. MILITARY SPECIFICATION FOR RED PHOSPHORUS

MIL-P-211B (June 18, 1969)

Characteristic	Percent by Weight			
	F[illegible] Graunulation		Extı ne Granulation	
	Minimum	Maximum	Minimum	Maximum
Red Phosphorus	99.0		99.0	
White Phosphorus		0.02		0.02
Acidity (as H_3PO_4)		0.10		0.10
Moisture		0.20		0.20
Particle Size:				
Retained on a No. 40 (420 micron) sieve				
Retained on a No. 100 (149 micron) sieve				2.0

Ref: (94)

TABLE 29

U. S. MILITARY SPECIFICATION FOR STYRENE-BUTADIENE RUBBER

MIL-R-51209 (MU), September 11, 1964

Property	Requirement	
	SBR type 1000	SBR type 1006
Volatile Matter, %	0.50 max.	0.50 max.
Ash, %	1.50 max.	1.50 max.
Fatty Acid (as Stearic Acid) %	4.00 to 6.25	3.75 to 6.00
Soap, %	0.75 max.	0.75 max.
Stabilizer, %	1.00 to 1.75	1.00 to 1.75
Bound Styrene, %	22.5 to 24.5	22.5 to 24.5
Mooney Viscosity, ML212°F at 4 minutes	46 to 52	46 to 54
Tensile Strength, psi, 50-minute cure at 292°F	2700 min	2500 min
Ultimate Elongation, 50-minute cure at 292°F	550 min	500 min
Modulus, psi, 300% elongation		
25 minute cure at 292°F	300 to 600	400 to 700
50 minute cure at 292°F	800 to 1150	900 to 1250
100 minute cure at 292°F	1250 to 1650	1400 to 1800

Ref: (95)

XXI. PLASTICIZED WHITE PHOSPHORUS SMOKE COMPOUND (WHITE PHOSPHORUS/BUTYL RUBBER)

Plasticized white phosphorus smoke compound is prepared from a granulated white phosphorus water slurry and styrene-butadiene rubber (plasticizer) in such a manner that the plasticized white phosphorus is a mixture of 75% white phosphorus and 25% styrene-butadiene rubber (96).

There is no information available relating to human toxicity, epidemiology, animal toxicity, metabolism or industrial hygiene and standards of plasticized white phosphorus. See sections XI-XIX for a discussion of white phosphorus and section XX for a discussion of styrene-butadiene rubber.

XXII. EPOXY WHITE PHOSPHORUS SMOKE COMPOUND (WHITE PHOSPHORUS/EPOXY RESIN)

Epoxy white phosphorus is compounded from white phosphorus and an epoxy resin, prepared by the interaction of epichlorohydrin with bis-(4-hydroxyphenyl)-dimethyl-methane (Bisphenol A). Epoxy resins are sometimes cured with a polyamine, a phenolic resin or an acid anhydride.

There is no information available in the literature regarding the toxicity of epoxy white phosphorus in humans or animals, nor are there data available on metabolism, epidemiology, industrial hygiene and standards. See sections XI-XIX for a discussion of white phosphorus.

HAZARDS TO HUMANS

The epoxy resin (Bisphenol A-epichlorohydrin) used by the U. S. Army is supplied by Speciality Plastics Co., Inc., Baltimore, Maryland, under the name of R-603 resin. The curing agent or hardener is also supplied by the same firm under the trade name H-36 and is a polyamine adduct. A personal communication (97) with the supplier indicated that both R-603 resin and H-36 hardener are mild skin sensitizers. An earlier report (98) has shown that no practical systemic hazard could be associated with exposure to vapors or by percutaneous absorption of Bisphenol A-epichlorohydrin resin.

TOXICITY OF COMBUSTION AND PYROLYSIS PRODUCTS OF EPOXY RESIN IN ANIMALS

Leong and MacFarland (99) have studied the hazards from exposure to combustion and pyrolysis products of Bisphenol A-epichlorohydrin resin in rats. The nature of pyrolysis or combustion products was not specified. A 20 g sample of the resin was burned and the combustion gases were introduced into a 300-liter chamber. Forty-eight Wistar rats were exposed to the combustion products for one hour. All animals survived and no pathological damage was associated with exposure to the combustion product of the epoxy resin (99).

Rats were exposed to pyrolysis products of the epoxy resin under the aforementioned conditions, using 1.0 - 16.0 g samples of the resin; there were no deaths when a 1.0 g sample was pyrolyzed. When the sample weight of the resin pyrolyzed was 1.4 g one out of 12 rats died after 72 hours. The mortality rate at various sample weights of the resin is given in Table 30. The principal cause of death in rats was respiratory failure from pulmonary edema. Other changes noted were histotoxic anoxia and systemic renal and hepatic changes (99).

Bisphenol A-epichlorohydrin resin has not been found to be carcinogenic in mice (98).

TABLE 30

CUMULATIVE DEATHS IN GROUPS OF 12 RATS

EXPOSED TO THE PYROLYSIS PRODUCTS OF EPOXY RESIN

Sample weight of the epoxy resin (g)	Cumulative Deaths at Indicated Time Point								Total Deaths
	Hour						Day		
	12	24	36	48	60	72	5	10	
1.0	--	--	--	--	--	--	--	--	0
1.4	--	--	--	--	--	1	--	--	1
2.0	--	--	3	4	--	5	--	--	5
2.9	1	3	5	7	8	10	--	--	10
4.2	1	8	9	11	--	--	--	--	11
6.0	3	11	12	--	--	--	--	--	12
10.5	8	9	11	--	--	12	--	--	12
16.0	12	--	--	--	--	--	--	--	12

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APPENDIX
INFORMATION SOURCES EXAMINED

Computer Searchable Data Bases

1. National Technical Information Services - covering 1964 to present (searched on 4/4/77).

2. Toxline/Toxback (searched on 3/29/77)

3. Chemical Condensates - covering 1972 to present (searched on 4/1/77)

4. BIOSIS Previews - covering 1972 to present (searched on 4/8/77)

5. ISI SCISEARCH - covering 1974 to present (searched on 4/8/77)

6. CANCERLINE (searched on 5/5/77)

7. NIOSH Technical Information Center file - (received on 5/15/77)

8. Defence Documentation Center - (received on 5/15/77)

Hard Bound Secondary References

1. Chemical Abstracts - V. 1 (1907) - V. 83 (1975).

2. Index Medicus - V.1 (1927) - V.18 (No. 4), 1977.

3. Excerpta Medica - sections entitled Toxicology and Pharmacology, Occupational Health and Industrial Medicine, Cancer, Environmental Health and Pollution Control (covering Vol. 1 through last volume available in 1976) were examined.

4. Engineering Index - (covering 1940 through 1977, issue #3).

5. Biological Abstracts - [covering Vol. 1 (1927) through Vol. 61 (1976)].

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